IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Japanese Application of

Tsuneji SUZUKI, et al.

Japanese Patent Application No.: 258863/1996

Japanese Patent Filing Date: September 30, 1996

for: "Cell Differentiation Inducer"

VERIFICATION OF TRANSLATION

Honorable Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

Jun NAKAGAWA residing at 3-7-21, Shibayama, Funabashi-shi, Chiba, Japan, declares:

(1) that he knows well both the Japanese and English languages;

(2) that he translated the above-identified Japanese Application from Japanese to English;

(3) that the attached English translation is a true and correct translation of the above-identified Japanese Application to the best of his knowledge and belief; and

(4) that all statements made of his own knowledge are true and that all statements made on information and belief and believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 USC 1001, and that such false statements may jeopardize the validity of the application or any patent issuing thereof.

December 3, 2002

Date

Jun Nakagawa

Jun NAKAGAWA

PATENT OFFICE

JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this office.

Date of Application: September 30, 1996

Application Number: Patent Application No. 1996-258863

Applicant(s): MITSUI TOATSU CHEMICALS, INC.

September 26, 1997

Commissioner, Toshimitsu ARAI (seal)

Patent Office

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[Title of the Invention] Novel Benzamide derivatives

[Number of Claims] 6

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[Representative] Akio SATO

[Indication of Official Fees]

[Advance Deposit Record Number] 010021

[Amount paid] 21000

[List of Materials Submitted]

[Material Name]	Specification	1
[Material Name]	Drawings	1
[Material Name]	Abstract	1

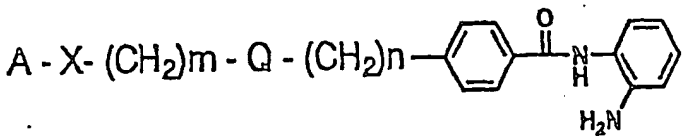
[Proof] Not Requested

[Document Name] Specification

[Title of the Invention] Novel Benzamide derivatives

[Claims]

[Claim 1] A benzamide derivative represented by the general formula (1):



(1)

[wherein A is an optionally substituted phenyl or an optionally substituted heterocyclic group which have 1 to 4 groups as a substituent(s) selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X represents a direct bond, $-O-$, $-S-$ or $-NH-$;

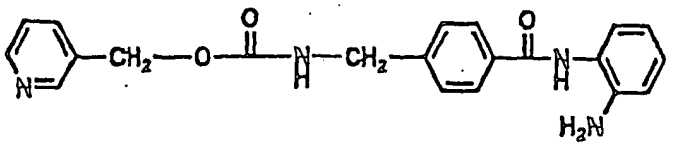
n and m are independently an integer of 0 to 4, provided that there is no case that both n and m are zero;

Q represents any one of an amido bond, a thioamido bond, an urethane bond, a thiourethane bond, an urea bond or a thiourea bond]

or a pharmaceutically acceptable salt thereof.

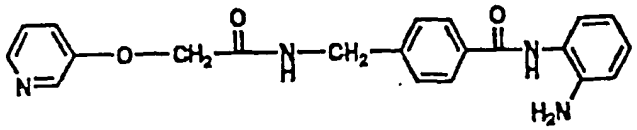
[Claim 2] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in Claim 1, wherein A is an optionally substituted pyridyl group.

[Claim 3] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in Claim 1, which is represented by the formula (2):



(2)

[Claim 4] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in Claim 1, which is represented by the formula (3):



(3)

[Claim 5] An anticancer agent comprising at least one of the compounds described in any one of Claims 1 to 4 as an active ingredient.

[Claim 6] A medical and pharmaceutical product comprising at least one of the compounds described in any one of Claims 1 to 4 as an active ingredient.

[Detailed Explanation of the Invention]

[0001]

[Industrial Field of the Invention]

This invention relates to a novel benzamide derivative. Further in detail, this invention relates to an anticancer agent based on the differentiation-inducing effect of the novel benzamide derivative and its uses for other medical and pharmaceutical products.

[0002]

[Prior Art]

Cancers have now become a top cause of death, exceeding heart and cerebrovascular diseases, and so many studies have been conducted with enormous expense and time to overcome cancers. They have not been, however, overcome in spite of a variety of investigations for therapy such as a surgical operation, a radiation therapy and thermotherapy. Among those therapies, chemotherapy is one of the main areas for cancer treatment. To date, however, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity and high therapeutic effect has been desired. Many of the conventional anticancer drugs show their effect by affecting mainly DNA to express their cytotoxicity and then injuring carcinoma cells. However, since they do not have sufficient selectivity between carcinoma cells and normal cells, adverse reactions expressed in normal cells have limited their use in therapy.

[0003]

Meanwhile, differentiation-inducing agents among anticancer drugs are aimed to induce differentiation of carcinoma cells for controlling their infinite proliferation, rather than directly kill the cells. The agents may, therefore, be inferior to the anticancer drugs directly killing carcinoma cells, with regard to involution of a carcinoma, but may be expected to have reduced toxicity and different selectivity. In fact, it is well known that retinoic acid, a differentiation-inducing agent, is used for treatment of acute promyelogenous leukemia, and is potent [Huang et al., Blood, 72, 567-572(1988); Castaign et al., Blood, 76, 1704-1709 (1990); Warrell et al., New Engl. J. Med. 324, 1385-1393(1991) etc.]. In addition, vitamin D derivatives exhibit differentiation-inducing effect, and thus their application for anticancer drugs have been investigated [e.g., Olsson et al, Cancer Res. 43, 5862-5867(1983) etc.].

[0004]

As the results of these investigations, there have been reported applications of a variety of differentiation-inducing agents such as vitamin D derivatives (JP-A 6-179622), isoprene derivatives (JP-A 6-192073), tocopherol (JP-A 6-256181), quinone derivatives (JP-A 6-305955), noncyclic polyisoprenoids (JP-A 6-316520), benzoic acid derivatives (JP-A 7-206765) and glycolipids (JP-A 7-258100), for anticancer drugs. There have been no agents having sufficient level of effect for cancer treatment in spite of the investigations, and thus there has been greatly desired a highly safe agent effective to a variety of cancers.

[0005]

[Problems to be solved by the Invention]

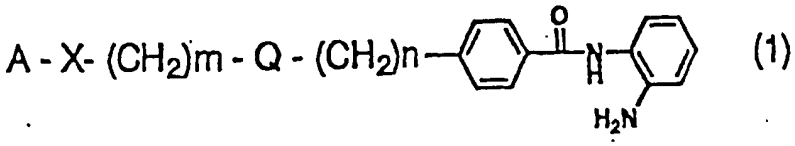
The object of the present invention is to provide compounds which exhibit differentiation-inducing effects and are useful as medical and pharmaceutical agents such as therapeutic or improving agents for malignant tumors, autoimmune diseases and dermatologic diseases.

[0006]

The present inventors intensely researched in order to achieve the object and have found that a novel benzamide derivative having differentiation-inducing effect show antitumor effect. As a result, this invention has been completed. Specifically, the present invention is:

[1] A benzamide derivative represented by the general formula (1):

[0007]



(1)

[wherein A is an optionally substituted phenyl or an optionally substituted heterocyclic group which have 1 to 4 groups as a substituent(s) selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X represents a direct bond, $-O-$, $-S-$ or $-NH-$;

n and m are independently an integer of 0 to 4, provided that there is no case that both n and m are zero;

Q represents any one of an amido bond, a thioamido bond, an urethane bond, a thiourethane bond, an urea bond or a thiourea bond]

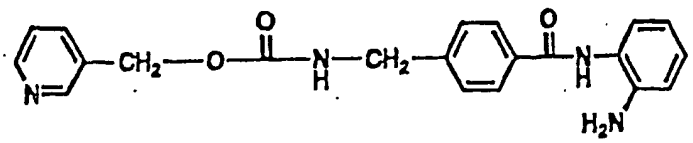
or a pharmaceutically acceptable salt thereof;

[0008]

[2] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in [1], wherein A is an optionally substituted pyridyl group;

[3] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in [1], which is represented by the formula (2);

[0009]

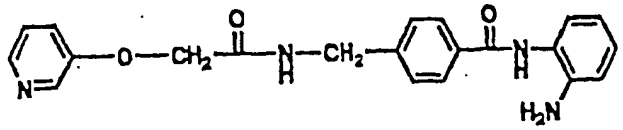


(2)

[4] A benzamide derivative or a pharmaceutically acceptable salt thereof as

claimed in [1], which is represented by the formula (3);

[0010]



(3)

[0011]

[5] An anticancer agent comprising at least one of the compounds described in any one of [1] to [4] as an active ingredient; and

[0012]

[6] A medical and pharmaceutical product comprising at least one of the compounds described in any one of [1] o [4] as an active ingredient.

[0013]

[Embodiments for carrying out the Invention]

The present invention is explained in detail below.

In the present invention, "1 to 4 carbons" means a carbon number per a single substituent; for example, for dialkyl substitution, it means 2 to 8 carbons.

A heterocycle in the compound represented by the general formula (1) may be a 5 or 6-membered ring containing 1 to 4 nitrogen, oxygen or sulfur atoms. Their examples include pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isoxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinuclidine, tetrahydrofuran, morpholine, thiomorpholine and the like.

[0014]

A halogen atom may be fluorine, chlorine, bromine or iodine atom.

An alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

[0015]

An alkoxy having 1 to 4 carbons includes methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

An aminoalkyl having 1 to 4 carbons includes aminomethyl, 1-aminoethyl, 2-aminopropyl and the like.

[0016]

An alkylamino having 1 to 4 carbons includes N-methylamino, N,N-dimethylamino, N,N-diethylamino, N-methyl-N-ethylamino, N,N-diisopropylamino and the like.

An acyl having 1 to 4 carbons includes acetyl, propanoyl, butanoyl and like.

[0017]

An acylamino having 1 to 4 carbons includes acetylamino, propanoylamino, butanoylamino and the like.

An alkylthio having 1 to 4 carbons includes methylthio, ethylthio, propylthio and the like.

A perfluoroalkyl having 1 to 4 carbons includes trifluoromethyl, pentafluoroethyl and the like.

[0018]

A perfluoroalkyloxy having 1 to 4 carbons includes trifluoromethoxy, pentafluoroethoxy and the like.

An alkoxycarbonyl having 1 to 4 carbons includes methoxycarbonyl and ethoxycarbonyl.

A pharmaceutically acceptable salt of the compound of this invention includes salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; and with an organic acid such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and the like, which are used generally in this field.

As used herein, a "medical and pharmaceutical product" in claim 6 includes a therapeutic and/or improving agent, for example, an anticancer drug, a drug against an autoimmune disease or dermatologic disease.

When it has an asymmetric carbon or carbons at "A" in the general formula (1), it may be present as an individual stereoisomer or a mixture of the stereoisomers including a racemic modification. This invention encompasses the above defined various forms, which may be also used as an active ingredient.

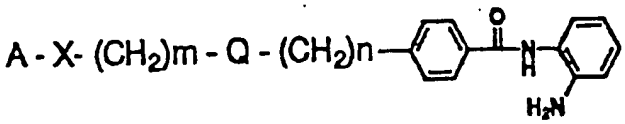
[0019]

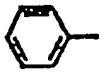
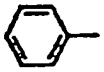
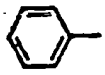
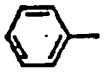
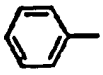
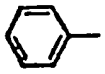
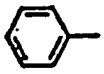
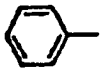
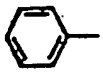
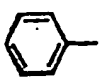
Representative compounds of this invention represented by the general formula (1) are specifically shown in Table 1, but this invention is not

intended to be limited to these.

[0020]

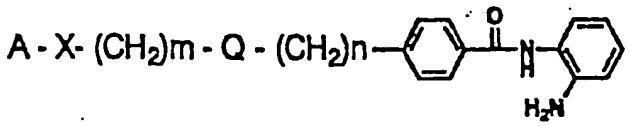
Table 1

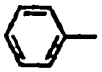
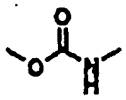
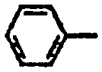
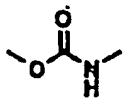
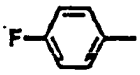
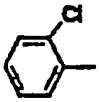
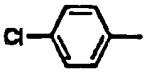
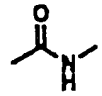
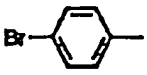
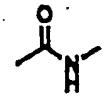
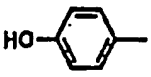
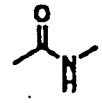
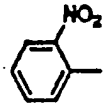
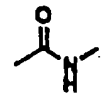
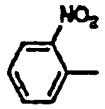
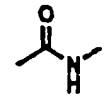
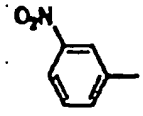
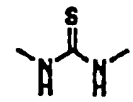


Compound No.	A	X	m	Q	n
1		Direct Bond	0		1
2		Direct Bond	1		0
3		Direct Bond	2		0
4		Direct Bond	3		0
5		Direct Bond	4		0
6		Direct Bond	1		1
7		Direct Bond	2		1
8		Direct Bond	1		0
9		Direct Bond	2		0
10		Direct Bond	0		1

[0021]

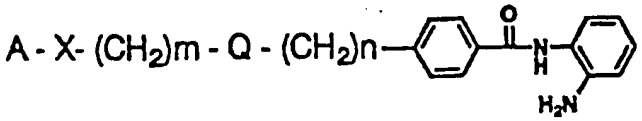
Table 1 (Cont.1)

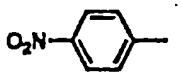
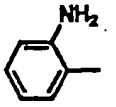
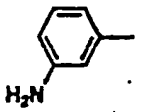
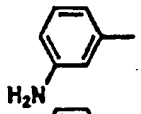
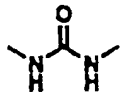
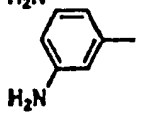
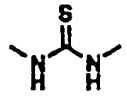
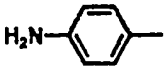
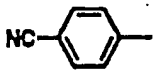
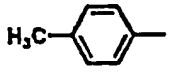
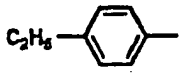
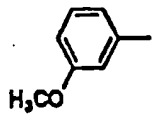


Compound No.	A	X	m	Q	n
11		Direct Bond	1		1
12		Direct Bond	0		1
13		Direct Bond	0		1
14		Direct Bond	0		1
15		Direct Bond	1		0
16		Direct Bond	0		1
17		Direct Bond	0		1
18		Direct Bond	0		1
19		Direct Bond	1		0
20		Direct Bond	0		1

[0022]

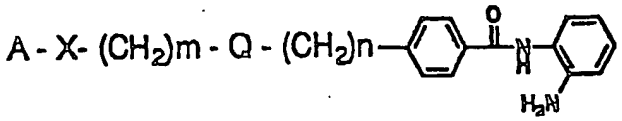
Table 1 (Cont. No. 2)

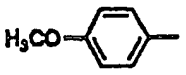
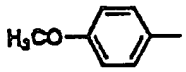
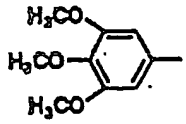
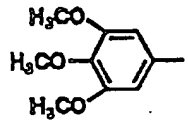
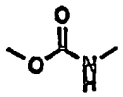
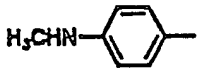
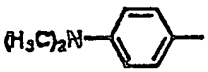
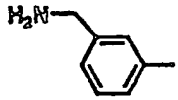
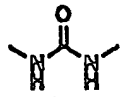
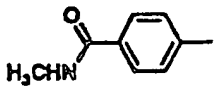
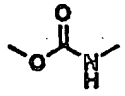
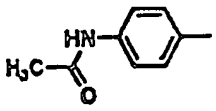
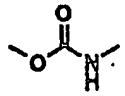
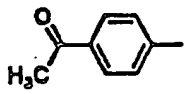


Compound No.	A	X	m	Q	n
2 1		Direct Bond	1		0
2 2		Direct Bond	1		0
2 3		Direct Bond	1		1
2 4		Direct Bond	0		1
2 5		Direct Bond	0		1
2 6		Direct Bond	1		0
2 7		Direct Bond	0		1
2 8		Direct Bond	0		1
2 9		Direct Bond	0		1
3 0		Direct Bond	0		1

[0023]

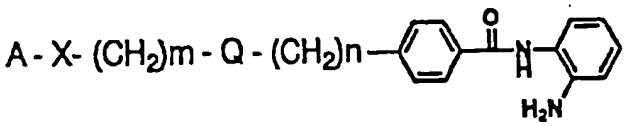
Table 1 (Cont. No. 3)

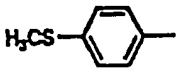
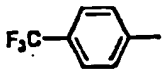
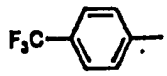
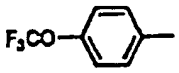
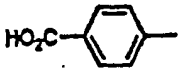
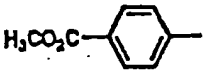
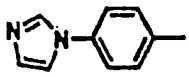
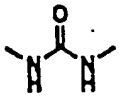
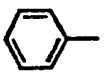
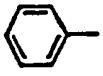
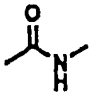
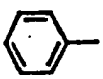


Compound No.	A	X	m	Q	n
3 1		Direct Bond	0		1
3 2		Direct Bond	1		0
3 3		Direct Bond	0		1
3 4		Direct Bond	1		1
3 5		Direct Bond	0		1
3 6		Direct Bond	0		1
3 7		Direct Bond	0		1
3 8		Direct Bond	1		1
3 9		Direct Bond	1		1
4 0		Direct Bond	0		1

[0024]

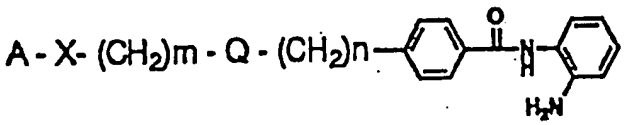
Table 1 (Cont. No. 4)

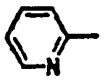
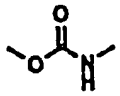
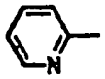
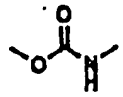
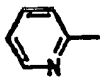
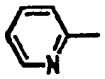
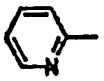
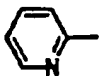
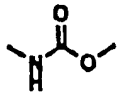
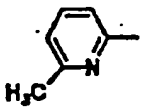
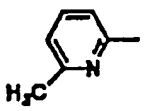
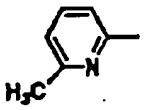
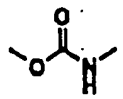
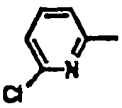
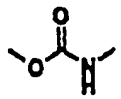


Compound No.	A	X	m	Q	n
4 1		Direct Bond	0		1
4 2		Direct Bond	0		1
4 3		Direct Bond	1		0
4 4		Direct Bond	0		1
4 5		Direct Bond	0		1
4 6		Direct Bond	0		1
4 7		Direct Bond	1		1
4 8		—O—	1		1
4 9		—S—	1		1
5 0		—N—	1		1

[0025]

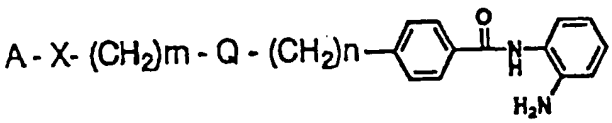
Table 1 (Cont. No. 5)

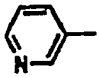
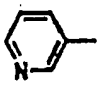
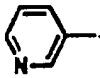
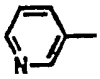
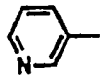
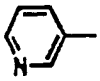
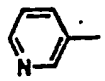
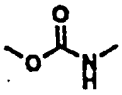
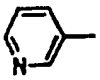
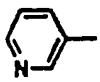
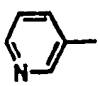
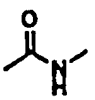


Compound No.	A	X	m	Q	n
5 1		Direct Bond	1		1
5 2		Direct Bond	2		1
5 3		Direct Bond	0		1
5 4		Direct Bond	1		0
5 5		Direct Bond	1		0
5 6		Direct Bond	1		1
5 7		Direct Bond	1		0
5 8		Direct Bond	0		1
5 9		Direct Bond	1		1
6 0		Direct Bond	1		1

[0026]

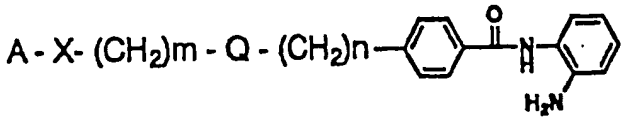
Table 1 (Cont. No. 6)

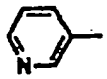
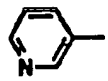
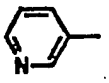
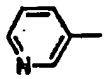
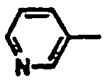
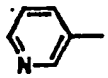
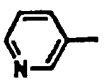
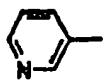
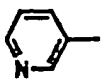


Compound No.	A	X	m	Q	n
61		—O—	1		1
62		—O—	2		1
63		—NH—	1		1
64		—S—	1		1
65		—O—	1		0
66		—O—	2		0
67		—O—	2		0
68		Direct Bond	1		0
69		Direct Bond	2		0
70		Direct Bond	3		0

[0027]

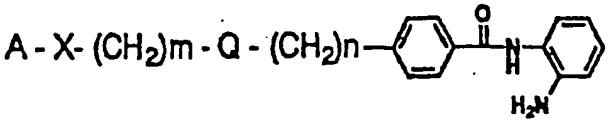
Table 1 (Cont. No. 7)

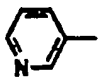
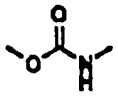
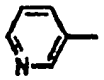
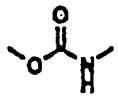
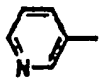
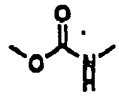
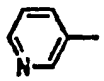
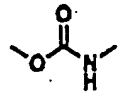
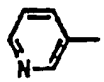
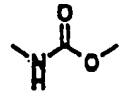
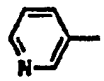
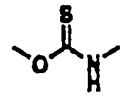
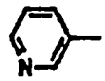
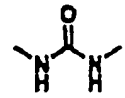
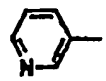
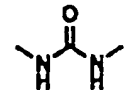
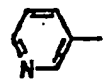
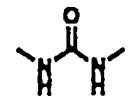
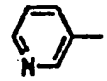
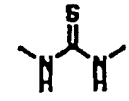


Compound No.	A	X	m	Q	n
7 1		Direct Bond	0		1
7 2		Direct Bond	0		2
7 3		Direct Bond	0		3
7 4		Direct Bond	1		1
7 5		Direct Bond	2		1
7 6		Direct Bond	3		1
7 7		Direct Bond	1		2
7 8		Direct Bond	1		1
7 9		Direct Bond	0		2
8 0		Direct Bond	1		2

[0028]

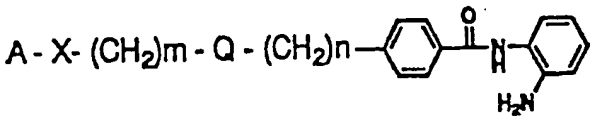
Table 1 (Cont. No. 8)

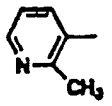
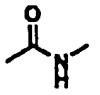
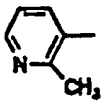
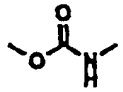
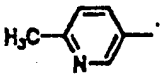
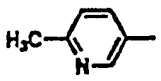
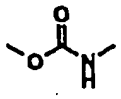
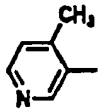
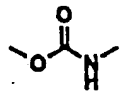
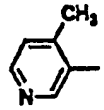
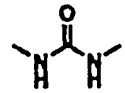
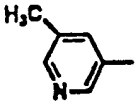
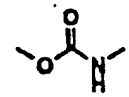
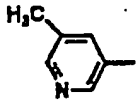
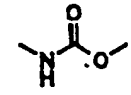
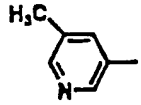
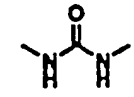
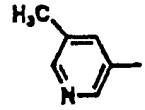
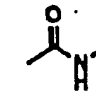


Compound No.	A	X	m	Q	n
8 1		Direct Bond	0		1
8 2		Direct Bond	1		1
8 3		Direct Bond	2		1
8 4		Direct Bond	3		1
8 5		Direct Bond	1		1
8 6		Direct Bond	1		1
8 7		Direct Bond	0		1
8 8		Direct Bond	1		1
8 9		Direct Bond	2		1
9 0		Direct Bond	1		1

[0029]

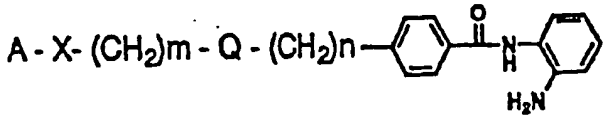
Table 1 (Cont. No. 9)

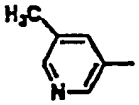
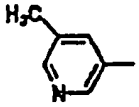
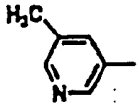
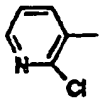
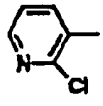
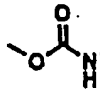
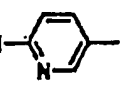
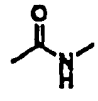
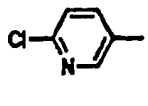
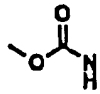
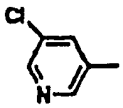
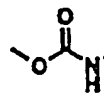
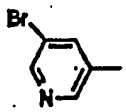
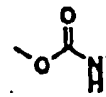


Compound No.	A	X	m	Q	n
9 1		Direct Bond	0		1
9 2		Direct Bond	1		1
9 3		Direct Bond	0		1
9 4		Direct Bond	1		1
9 5		Direct Bond	1		1
9 6		Direct Bond	1		1
9 7		Direct Bond	1		1
9 8		Direct Bond	1		1
9 9		Direct Bond	1		1
1 0 0		Direct Bond	2		1

[0030]

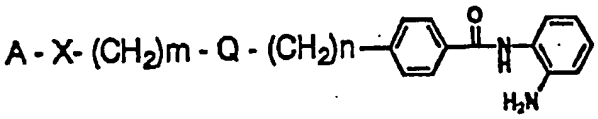
Table 1 (Cont. No. 10)

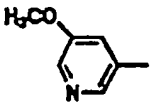
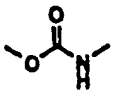
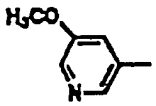
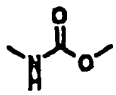
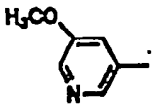
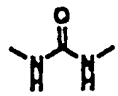
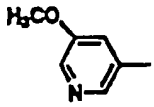
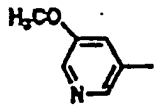
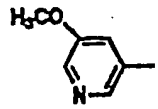
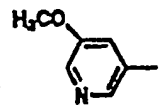
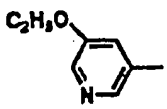
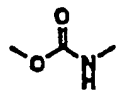
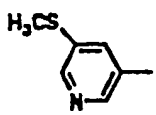
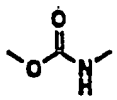
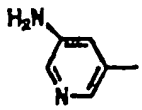
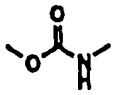


Compound No.	A	X	m	Q	n
101		Direct Bond	2		1
102		Direct Bond	2		0
103		Direct Bond	1		2
104		Direct Bond	0		1
105		Direct Bond	1		1
106		Direct Bond	1		1
107		Direct Bond	0		1
108		Direct Bond	1		1
109		Direct Bond	1		1
110		Direct Bond	1		1

[0031]

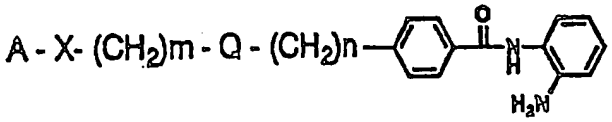
Table 1 (Cont. No. 11)

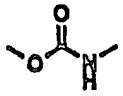
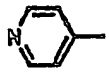
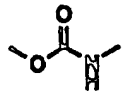
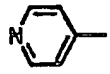
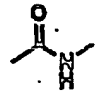
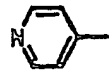
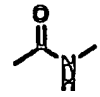
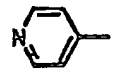
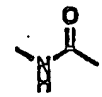
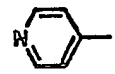
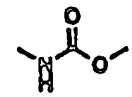
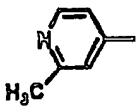
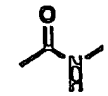
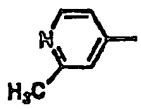
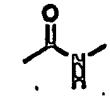
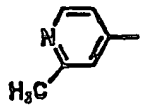
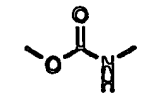
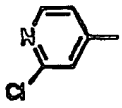
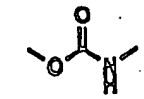


Compound No.	A	X	m	Q	n
111		Direct Bond	1		1
112		Direct Bond	1		1
113		Direct Bond	1		1
114		Direct Bond	2		1
115		Direct Bond	2		1
116		Direct Bond	2		0
117		Direct Bond	1		2
118		Direct Bond	1		1
119		Direct Bond	1		1
120		Direct Bond	1		1

[0032]

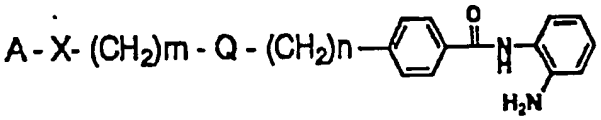
Table 1 (Cont. No. 12)

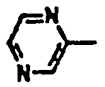
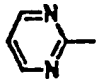
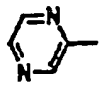
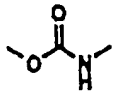
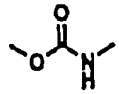
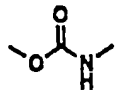
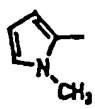


Compound No.	A	X	m	Q	n
121		Direct Bond	1		1
122		Direct Bond	2		1
123		Direct Bond	0		1
124		Direct Bond	1		0
125		Direct Bond	1		0
126		Direct Bond	1		1
127		Direct Bond	1		0
128		Direct Bond	0		1
129		Direct Bond	1		1
130		Direct Bond	1		1

[0033]

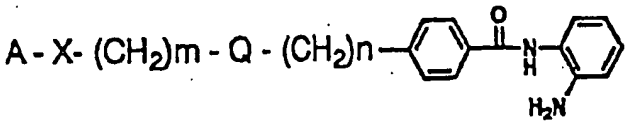
Table 1 (Cont. No. 13)

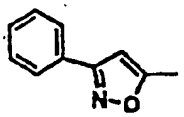
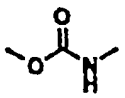
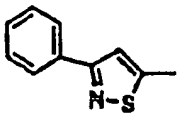
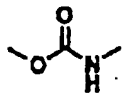
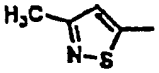
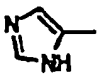
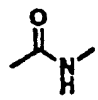
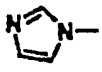
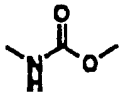
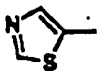
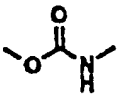
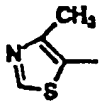
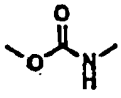
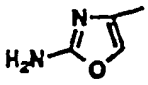
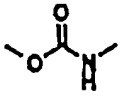
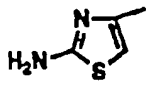
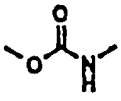


Compound No.	A	X	m	Q	n
131		Direct Bond	0		1
132		Direct Bond	0		1
133		Direct Bond	0		1
134		Direct Bond	0		1
135		Direct Bond	1		1
136		Direct Bond	2		1
137		Direct Bond	0		1
138		Direct Bond	1		1
139		Direct Bond	0		1
140		Direct Bond	0		1

[0034]

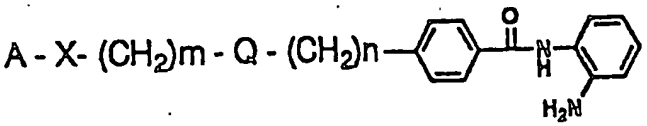
Table 1 (Cont. No. 14)

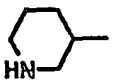
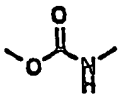
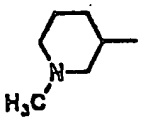
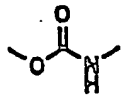
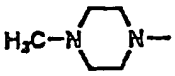
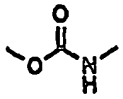
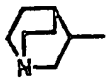
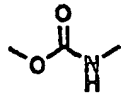
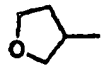
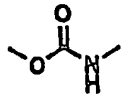
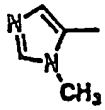
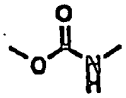
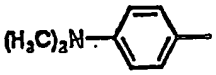
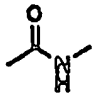
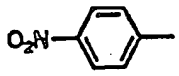
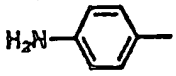


Compound No.	A	X	m	Q	n
141		Direct Bond	1		1
142		Direct Bond	1		1
143		Direct Bond	0		1
144		Direct Bond	0		1
145		Direct Bond	0		1
146		Direct Bond	3		1
147		Direct Bond	1		1
148		Direct Bond	2		1
149		Direct Bond	1		1
150		Direct Bond	1		1

[0035]

Table 1 (Cont. No. 15)



Compound No.	A	X	m	Q	n
151		Direct Bond	1		1
152		Direct Bond	1		1
153		Direct Bond	3		1
154		Direct Bond	1		1
155		Direct Bond.	1		1
156		Direct Bond	1		1
157		Direct Bond	1		0
158		—O—	1		0
159		—O—	1		0

[0036]

The compound of this invention may be prepared, for example, as described below.

(a) A compound represented by the general formula (4);

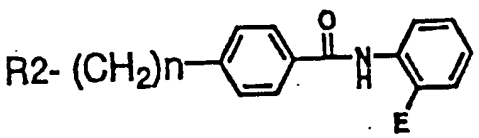
[0037]

$$A\text{-}X\text{-}(CH_2)m\text{-}R1 \qquad (4)$$

wherein A, X and m are as defined above; R1 is -C(=G)OH (G is an oxygen or sulfur atom) or $-NH_2$;

is condensed with a compound represented by the general formula (5);

[0038]



(5)

wherein n is as defined as above; R2 is $-NH_2$ when R1 is -C(=G)OH (G is an oxygen or sulfur atom) and -C(=G)OH (G is an oxygen or sulfur atom) when R1 is $-NH_2$; E is an amino group bound with a protective group used in a common peptide-forming reaction, e.g., tert-butoxycarbonyl.

Alternatively,

(b) a compound represented by the general formula (6)

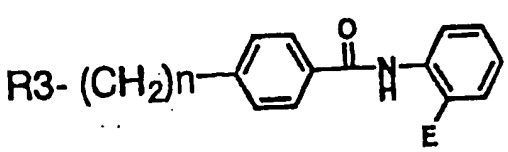
[0039]

$$A\text{-}X\text{-}(CH_2)m\text{-}R3$$

wherein A, X and m are as defined above; and R3 is -OH or $-NH_2$;

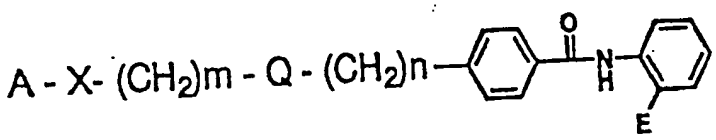
is condensed with a compound represented by the general formula (7);

[0040]



(7)

wherein R3, n and E are as defined above;
by using an agent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, phosgene or thiophosgene, to give a compound represented by the general formula (8):
[0041]

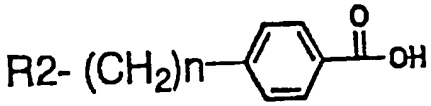


(8)

wherein A, X, m, Q, n and E are as defined above;
and the protecting group is then removed from it to give the desired compound.

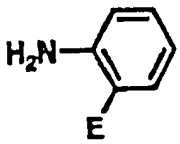
The compound represented by the general formula (4) is commercially available or may be produced by the method in the example described later.

The compound of the general formula (5) may be obtained by introducing a suitable protecting group into a benzoic acid derivative represented by the general formula (9):
[0042]



(9)

wherein R2 and n are defined as above;
subjecting the resulting product to condensation with a compound represented by the general formula (10):
[0043]



(10)

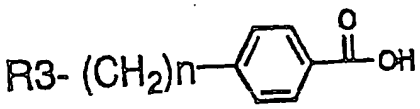
wherein E is defined as above;
and leaving the protecting group.

[0044]

The compound of the general formula (6) is commercially available or may be produced by the method in the example described later.

The compound represented by the general formula (7) can be obtained by introducing a suitable protecting group in to a benzoic acid derivative represented by the general formula (11):

[0045]



(11)

wherein R3 and n are defined as above;
subjecting the resulting product to condensation with a compound represented by the general formula (10) and leaving the protecting group.

The compound represented by the general formula (11) is commercially available or may be produced by the method in the example described later.

[0046]

The condensation reaction in (a) may be an amido-bond forming reaction for a usual peptide using, for example, an activated ester, a mixed acid anhydride or an acid chloride. For example, a carboxylic acid, i.e., a compound represented by the general formula (4) wherein R1 is $-C(=G)OH$ (G is an oxygen or sulfur atom) or a compound represented by the general formula (5) wherein R2 is $-C(=G)OH$ (G is an oxygen or sulfur atom), may be condensed with a phenol derivative such as 2,4,5-trichlorophenol, pentachlorophenol or 4-nitrophenol, or an N-hydroxy compound such as N-hydoxysuccinimide or N-hydroxybenzotriazole, in the presence of dicyclohexylcarbodiimide, to be converted into an activated ester, which is then condensed with an amine represented by the general formula (4) wherein R1 is $-NH_2$ or by the general formula (5) wherein R2 is $-NH_2$, to give the desired product.

[0047]

Alternatively, a carboxylic acid represented by the general formula (4) wherein R1 is $-C(=G)OH$ (G is an oxygen or sulfur atom) or by the general formula (5) wherein R2 is $-C(=G)OH$ (G is an oxygen or sulfur atom), may be reacted with, for example, oxalyl chloride, thionyl chloride or phosphorus oxychloride to be converted into an acid chloride, which is then condensed with an amine represented by the general formula (4) wherein R1 is $-NH_2$ or by the general formula (5) wherein R2 is $-NH_2$, to give the desired product.

[0048]

Furthermore, a carboxylic acid represented by the general formula (4) wherein R1 is $-C(=G)OH$ (G is an oxygen or sulfur atom) or by the general formula (5) wherein R2 is $-C(=G)OH$ (G is an oxygen or sulfur atom), may be reacted with, for example, isobutyl chlorocarbonate or methanesulfonyl chloride to be converted into a mixed acid anhydride, which is then condensed with an amine represented by the general formula (4) wherein R1 is $-NH_2$ or by the general formula (5) wherein R2 is $-NH_2$, to give the desired product.

The above condensation reaction may be conducted solely using a peptide condensing agent such as dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, diphenyl phosphoric azide, diethylphosphorylcyanide, etc.

[0049]

The reaction may be usually conducted at -20 to $+50$ ℃ for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; N,N-dimethylformamide; alcohols such as methanol, ethanol and the like; and a mixture thereof. If necessary, an organic base such as triethylamine or pyridine may be added.

[0050]

The condensation reaction in (b) may be conducted by activating a compound represented by either the general formula (6) or (7) with, for example, phosgene, thiophosgene, N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole or the like and then reacting the activated product with the other compound. The reaction may be usually conducted at

−20 to +50 ℃ for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; N,N-dimethylformamide; and a mixture thereof. If necessary, an organic base such as triethylamine, pyridine and the like may be added.

[0051]

Removal of the protecting group in the compound represented by the general formula (8) is carried out under the condition used in the general reaction for peptide production. For example, when E in the general formula (8) is the amino group protected with tert-butoxycarbonyl, the removal reaction of the protecting group can be carried out by treatment with an acid such as hydrochloric acid or the like.

[0052]

A salt of a compound represented by the general formula (1) may be formed during preparation of the compound of the general formula (1), but is usually formed with a pharmaceutically acceptable acid. Such an acid includes inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; and organic acids such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and the like. These salts may be also used as an active ingredient in this invention, as the free form of the compound represented by the general formula (1).

[0053]

A compound represented by the general formula (1) may be purified or isolated by a usual separation method such as extraction, recrystallization, column chromatography and the like.

[0054]

The novel benzamide derivative of this invention has differentiation-inducing effect and thus is useful as a therapeutical and improving agent to a variety of diseases such as malignant tumors, autoimmune diseases and dermatologic diseases.

As used herein, a "malignant tumor" includes hematologic malignancy such as acute leukemia, chronic leukemia, malignant lymphoma, multiple

myeloma or macroglobulinemia as well as solid tumors such as colon cancer, cerebral tumor, head and neck tumor, breast carcinoma, pulmonary cancer, esophageal cancer, gastric cancer, hepatic cancer, gallbladder cancer, bile duct cancer, pancreatic cancer, nesidioblastoma, renal cell carcinoma, adrenocortical cancer, urinary bladder carcinoma, prostatic cancer, testicular tumor, ovarian carcinoma, uterine cancer, chorionic carcinoma, thyroid cancer, malignant carcinoid tumor, skin cancer, malignant melanoma, osteogenic sarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumor and retinoblastoma.

An autoimmune disease shows rheumatism, nephritis and diabetes.

The dermatologic diseases include psoriasis, acne, exanthema and atopic dermatitis.

The diseases to be targeted by the present invention are not limited to these specific examples.

[0055]

The active ingredient compounds of this invention are useful as a drug, which may be used in the form of a general pharmaceutical composition. The pharmaceutical composition may be prepared with generally used diluents or excipients such as filler, extender, binder, moisturizing agent, disintegrator, surfactant and lubricant. The dosage form of the pharmaceutical composition may be selected from a variety of dosage forms depending on its therapeutic purpose; typically tablet, pill, powder, solution, suspension, emulsion, granule, capsule, injection (e.g., solution, suspension) and suppository.

[0056]

For preparing tablets, a variety of carriers well-known in the art may be widely used. Such a carrier includes excipients such as lactose, sucrose, sodium chloride, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate and polyvinyl pyrrolidone;

[0057]

disintegrators such as dried starch, sodium alginate, powdered agar, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid

esters, sodium lauryl sulfate, stearic acid monoglyceride, starch and lactose; disintegration retarders such as sucrose, stearic acid, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch; adsorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates, bronic acid powder and polyethylene glycol. The tablet may be, if necessary, one coated with a common coating; for example, sugar-coated tablet, gelatin-coated tablet, enteric coated tablet, film-coated tablet, and the tablet may be a double-layer tablet or multilayer tablet.

[0058]

In forming pills, a variety of carriers well-known in the art may be widely used. Such a carrier includes excipients such as glucose, lactose, starch, cacao-oil, hydrogenated vegetable oil, kaoline and talc; binders such as powdered acacia gum, powdered tragacanth gum and gelatin; disintegrators such as calcium carmelose and agar.

Capsule may be prepared by blending an active ingredient with a variety of the above carriers as usual and filling the resulting blend into, for example, a hard gelatin or soft capsule or the like.

[0059]

For preparing injection, solution, emulsion and suspension are sterilized and preferably isotonic with blood. It may be prepared using diluents commonly used in the art; for example, water, ethanol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. The pharmaceutical preparation may contain sodium chloride, glucose or glycerin necessary to prepare an isotonic solution, as well as usual solubilizers, buffers and soothing agents may be added.

[0060]

Suppository may be formed by widely using a variety of well-known carriers; for example, polyethylene glycol, cacao oil, higher alcohols, higher alcohol esters, gelatin and semi-synthetic glyceride.

Furthermore, the pharmaceutical composition may contain coloring agents, preservatives, perfumes, flavors, sweeteners or other drugs.

The amount of the active ingredient in the pharmaceutical composition of this invention may be, as appropriate, selected from a wide range with no limitations, and is generally about 1 to 70 % by weight in the composition, preferably about 5 to 50 % by weight.

[0061]

An administration route of the pharmaceutical composition is not limited, and selected depending on its composition form, patient's age, sex, severity of disease and other conditions. For example, tablet, pill, solution, suspension, emulsion, granule and capsule may be orally administered; injection may be intravenously administered solely or in combination with a common infusion fluid such as glucose, amino acids and the like, or if necessary, intramuscularly, subcutaneously or intraperitoneally as a sole preparation. Suppository may be intrarectally administered.

[0062]

Dose of the pharmaceutical preparation of this invention may be selected, depending on their dosage form, patient's age, sex and severity of disease, and other conditions, as appropriate, but the amount of the active ingredient may be generally about 0.0001 to 100 mg/kg a day. It is recommended that a unit dosage form may contain about 0.001 to 1000 mg of the active ingredient.

The compound represented by the general formula (1) of this invention or a salt thereof exhibits no toxicity at the dose showing pharmacological effects.

[0063]

[Examples]

This invention will be specifically illustrated with, but is not limited to, the following examples. The numbers in parentheses indicate those of the compounds are those shown in the above detailed description.

Example 1

Preparation of N-(2-aminophenyl)-4-(N-benzoylaminomethyl) benzamide hydrochloride (Table 1: hydrochloride of Compound 1):

[0064]

(1-1) To a suspension of 4-aminomethylbenzoic acid(21.16 g, 140 mmol) in dichloromethane (450 ml) was added triethylamine (42 ml, 300 mmol).

Under ice-cooling, trifluoroacetic anhydride (60.4 g, 287 mmol) in dichloromethane (50 ml) were added dropwise, maintaining the inner temperature at 3 to 8 ℃, and then the mixture was stirred four 3 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution, and was acidified with 10 % hydrochloric acid. The gel precipitate was collected by filtration and dried to give 4-(N-trifluoroacetylaminomethyl) benzoic acid (30.4 g, Yield: 87.8 %) as an opalescent solid.
1H NMR (270 MHz, DMSO-d6) δ ppm: 4.47(2H, d, 5.8), 7.39(2H, d, 8.1), 7.93(2H, d, 8.1), 10.08(1H, t, 5.8), 12.95(1H, br.s.)
[0065]

(1-2) To a solution of o-phenylenediamine (54.0 g, 500 mmol) in dioxane (500 ml) was added 1N sodium hydroxide aq.(250 ml), and then di-tert-butoxy dicarbonate (109.1 g, 550mmol) in dioxane (250 ml) under ice-cooling. After stirring for 6 hours at room temperature, the mixture was left overnight. The mixture was concentrated to 1/2 volume by evaporation, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography (eluent: chloroform) to give a solid, which was then washed with diethyl ether to give N-tert-butoxycarbonyl-o-phenylenediamine (34.2 g, Yield: 32.8 %) as a white solid.
1H NMR (270 MHz, CDCl3) δ ppm: 1.51(9H, s), 3.75(2H, s), 6.26(1H, s), 6.77(1H, d, J=8.1 Hz), 6.79(1H, dd, J=7.3, 8.1 Hz), 7.00(1H, dd, J=7.3, 8.1 Hz), 7.27(1H, d, J=8.1 Hz)
[0066]

(1-3) To a suspension of the compound from the process (1-1) (30 g, 121 mmol) in dichloromethane (200 ml) were slowly added dropwise oxalyl chloride (21 g, 165 mmol) with intermittently adding DMF (0.1 ml per 2 ml addition), maintaining the inner temperature within 10 to 15 ℃ by ice-cooling. After completion of the addition, the mixture was stirred until bubble generation ceased, and then at 40 ℃ for an additional hour. After evaporation, excess oxalyl chloride was azeotropically removed with toluene, and then the residue was redissolved in dichloromethane (100 ml). The prepared acid chloride solution was added dropwise to a solution of the compound from the process (1-2) (22.88 g, 110 mmol) in dichloromethane (100

ml) and pyridine (200 ml), maintaining the inner temperature within 7 to 9 ℃ by ice-cooling.

[0067]

After addition, the mixture was warmed to room temperature, and was left overnight. After adding saturated sodium bicarbonate aq. to the reaction mixture, the resulting mixture was extracted with chloroform, and the organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give N-[2-(N-tert-butoxycarbonyl) aminophenyl]-4-trifluoroacetylaminomethylbenzamide (28.1 g, Yield: 58 %) as a light yellow solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 1.44(9H, s), 4.48(2H, d, 5.9), 7.12-7.23(2H, m), 7.44(2H, d, 8.1), 7.54(2H, d, 8.1), 7.94(2H, d, 8.1), 8.68(1H, br.s), 9.83(1H, s), 10.10(1H, br.t, 5.9)

[0068]

(1-4) To a suspension of the compound from the process (1-3) (13.12 g, 30 mmol) in methanol (120 ml) and water (180 ml) were added potassium carbonate (4.70 g, 34.0 mmol), and the mixture was heated with stirring at 70 ℃ for 4 hours. It was extracted with chloroform, and the organic layer was washed with saturated brine, dried, evaporated and dried to give 4-aminomethyl-N-[2-(N-tert-butoxycarbonyl)aminophenyl]benzamide (10.3 g, Yield: quantitative) as a light yellow amorphous solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 3.80(2H, s), 7.13-7.23(2H, m), 7.48-7.58(4H, m), 7.90(2H, d, 8.1), 8.69(1H, br.s), 9.77(1H, br.s)

[0069]

(1-5) To a solution of the compound from the process (1-4) (0.11 g, 0.44 mmol) in pyridine (5 ml) was added benzoyl chloride (0.08 g, 0.53 mmol) under ice-cooling, and the mixture was gradually warmed to room temperature and then stirred for 8 hours. Saturated sodium bicarbonate aq. was added, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether, and the solid obtained was dried to give N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(N-benzoylaminomethyl)benzam ide (0.14 g, Yield: 71.4 %) as a white solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 1.44(9H, s), 4.56(2H, d, 5.9), 7.11-7.22(2H, m), 7.46-7.56(7H, m), 7.90-7.94(4H,m), 8.67(1H, s), 9.15(1H, t, 5.9), 9.81(1H, s)

[0070]

(1-6) To a solution of the compound from the process (1-5) (0.10 g, 0.224 mmol) in dioxane (5 ml) and methanol (1 ml) was added 4N hydrochloric acid-dioxane (5 ml), and the mixture was stirred at room temperature for 7 hours. To the residue after evaporation was added diisopropyl ether, and the formed solid was collected by filtration and dried to give N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (0.08 g, Yield: 93 %) as a light brown solid.

mp: 206-209 ℃

1H NMR (270 MHz, DMSO-d6) δ ppm: 4.57(2H, d, 5.8), 7.27-7.38(4H, m), 7.47-7.59(5H, m), 7.92(1H, d, 8.1), 8.05(1H, d, 8.1), 9.19(1H, t, 5.8), 10.38(1H, br.s)

IR(KBr, cm-1): 3286, 3003(br.), 1630, 1551, 1492, 1306, 1250, 749, 695.

As described in Example 1, the compounds of Examples 2 to 30 were prepared, each of whose melting point (mp), 1H NMR data, IR data are described below.

[0071]

Example 2

N-(2-aminophenyl)-4-[N-(2-chlorobenzoyl)aminomethyl]benzamide (Table 1: Compound 14)

mp: 201-204 ℃(dec.).

1H NMR (270MHz, DMSO-d6) δ ppm: 4.52(2H, t, 5.9), 4.89(2H, br.s), 6.60(1H, ddd, 1.5, 7.3, 8.1), 6.78(1H, dd, 1.5, 8.1), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.17(1H, d, 8.1), 7.38-7.54(6H,m), 7.97(2H, d, 8.1), 9.06(1H, br.t, 5.9), 9.63(1H, br.s)

IR (KBr) cm-1: 3268, 1649, 1458, 1304, 748

[0072]

Example 3

N-(2-aminophenyl)-4-[N-(2-nitrobenzoyl)aminomethyl]benzamide hydrochloride(Table 1: hydrochloride of Compound 18)

mp: 210-212 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm : 4.55(2H, t, 5.9), 7.20-7.40(3H, m),

7.50-7.6(1H, m), 7.53(2H, d, 8.1), 7.60-7.70(2H, m), 7.83(1H, ddd, 1.5, 8.1, 8.1), 8.00-8.10(3H, m), 9.34(1H, t, 5.9), 10.43(1H, br.s)

IR(KBr)cm-1 :3283, 2500-3000(br.), 1648, 1534, 1461, 1362, 1314, 754, 701

[0073]

Example 4

N-(2-aminophenyl)-4-[N-(4-methylbenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 28)

mp:(amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm : 2.37(3H, s), 4.56(2H, d, 5.0), 7.20-7.30(6H, m), 7.47(4H, d, 8.8), 7.82(2H, d, 8.8), 8.03(2H, d, 8.8), 9.09(1H, t, 5), 10.36(1H, br.s)

IR(KBr)cm-1:3269(br.), 2861(br.), 1743, 1636, 1534, 1505, 1456, 1308, 1120, 753.

[0074]

Example 5

N-(2-aminophenyl)-4-[N-(3-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 30)

mp: 182-185 ℃

1H NMR(270MHz, DMSO-d6) δppm: 3.81(3H, s), 4.54(2H,d, 5.9), 4.88(2H, br.s) , 6.60(1H, dd, 6.6, 7.3), 6.78(1H, d, 7.3), 6.97(1H, dd, 6.6, 7.3), 7.11(1H, dd, 1.5, 8.1), 7.16(1H, d, 7.3), 7.35-7.51(5H, m), 7.94(2H, d, 8.1), 9.12(1H, br.t, 5.9), 9.63(1H, br.s)

IR(KBr)cm-1: 3301, 1637, 1524, 1489, 1457, 1314, 1248, 752

[0075]

Example 6

N-(2-aminophenyl)-4-[N-(4-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 31)

mp: 149-151 ℃

1H NMR(270MHz, DMSO-d6) δppm: 3.82(3H, s), 4.53(2H, d, 5.9), 4.88(2H, s), 6.59(1H, dd, 7.3, 7.3), 6.77(1H, d, 8.1), 6.94-7.00(1H,m), 7.02(2H, d, 8.8), 7.16(1H, d, 8.1), 7.43(2H, d, 8.1), 7.89(2H, d, 8.8), 7.94(2H, d, 8.1), 8.98(1H, br.t, 5.9), 9.61(1H, br.s)

IR(KBr)cm-1: 3297, 1630, 1527, 1505, 1457, 1256, 1177, 1024, 843, 749

[0076]

Example 7

N-(2-aminophenyl)-4-[N-(3,4,5-trimethoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 33)

mp: 208-210 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 3.71(3H, s), 3.83(6H, s), 4.55(2H, d, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, dd, 6.6, 8.1), 7.16(1H, d, 8.1), 7.26(2H, s), 7.44(2H, d, 8.1), 7.95(2H, d, 8.8), 9.07(1H, t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3267, 1635, 1582, 1457, 1237, 1132, 755

[0077]

Example 8

N-(2-aminophenyl)-4-[N-[4-(N,N-dimethyl)aminobenzoyl]aminomethyl]benzamide (Table 1: Compound 36)

mp: 216-219 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 2.98(6H, s), 4.51(2H, d, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 8.1, 8.1), 6.71(2H, d, 8.8), 6.97(1H, ddd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.41(2H, d, 8.1), 7.78(2H, d, 8.8), 7.93(2H, d, 8.1), 8.77(1H, t, 5.9), 9.63(1H, br.s).

IR(KBr)cm-1: 3301, 1632, 1519, 1457, 1298, 754

[0078]

Example 9

N-(2-aminophenyl)-4-[N-(4-trifluoromethylbenzoyl)aminomethyl]benzamide (Table 1: Compound 42)

mp: 243-246 ℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H, d, 5.9), 4.88(2H,br.s), 6.59(1H,dd, 6.6, 7.3), 6.77(1H, d, 8.1), 6.94(1H, dd, 5.9, 6.6), 7.16(1H, d, 8.1), 7.45(2H, d, 8.1), 7.88(2H, d, 8.8), 7.95(2H, d, 8.1), 8.11(2H, d, 8.1), 9.38(1H, t, 5.9), 9.64(1H, br.s)

IR(KBr)cm-1: 3301, 1640, 1549, 1523, 1458, 1334, 1162, 1120, 1070, 856, 750

[0079]

Example 10

N-(2-aminophenyl)-4-[N-(4-carboxybenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 45)

mp: (amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H, d, 5.9), 7.29-7.37(3H, m), 7.49(3H, d, 8.1), 8.02-8.06(6H, m), 9.36(1H, t, 5.9), 10.4(1H, br.s)
IR(KBr)cm-1: 3432(br.), 1718, 1637, 1542, 1499, 1303(br.), 1116, 1018, 757
[0080]
Example 11
N-(2-aminophenyl)-4-[N-(4-methoxycarbonylbenzoyl)aminomethyl]benzamide (Table 1: Compound 46)
mp: 204-209 ℃(dec.)
1H NMR(270MHz, DMSO-d6) δ ppm: 3.89(3H, s), 4.57(2H, d, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 6.6, 7.3), 6.78(2H,d, 7.3), 6.97(1H, ddd, 1.5, 6.6, 7.3), 7.16(1H, d, 7.3), 7.45(2H, d, 8.1), 7.95(2H, d, 8.1), 8.03(2H, d, 8.8), 8.07(2H, d, 8.8), 9.35(1H, t, 5.9), 9.64(1H, br.s)
IR(KBr)cm-1: 3287(br.), 1721, 1634, 1281, 1113, 750, 703
[0081]
Example 12
N-(2-aminophenyl)-4-(N-picolinoylaminomethyl)benzamide (Table 1: Compound 53)
mp: 173-178 ℃(dec.)
1H NMR(270MHz, DMSO-d6) δ ppm: 4.57(2H, d, 6.6), 4.88(2H,br.s), 6.59(1H, dd, 7.3, 8.1), 6.77(1H, d, 8.1), 6.96(1H, dd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.44(2H, d, 8.1), 7.60-7.65(1H, m), 7.93(2H, d, 8.1), 7.98-8.08(2H, m), 8.67(1H, d, 4.4), 9.45(1H, t, 6.6), 9.61(1H, br s)
IR(KBr)cm-1: 3330, 1656, 1634, 1523, 1456, 1294, 752
[0082]
Example 13
N-(2-aminophenyl)-4-[N-(6-methylpicolinoyl)aminomethyl]benzamide (Table 1: Compound 58)
mp: 172-173 ℃
1H NMR(270MHz, DMSO-d6) δ ppm: 2.51(3H, s), 4.57(2H,d, 6.6), 5.0(2H, br.s), 6.61(1H, dd, 7.3, 8.1), 6.79(1H, d, 7.3), 6.98(1H, dd, 7.3, 8.1), 7.17(1H, d, 7.3), 7.44(2H, d, 8.1), 7.43-7.49(1H, m), 7.84-7.90(2H, m), 7.94(2H, d, 8.1), 9.27(1H, t, 5.9), 9.64(1H, br.s)
IR(KBr)cm-1: 3331, 1675, 1634, 1594, 1523, 1454, 1307, 1292, 750
[0083]

Example 14

N-(2-aminophenyl)-4-(N-nicotinoylaminomethyl)benzamide (Table 1: Compound 71)

mp: 193-196 ℃

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H, d), 4.88(2H, br.s), 6.60(1H, t), 6.78(1H, d), 6.97(1H, t), 7.16(1H, d), 7.46(2H, d), 7.53(1H, dd), 7.95(2H, d), 8.24(1H,ddd), 8.73(1H,dd), 9.07(1H,d), 9.32(1H,br.t), 9.63(1H, br.s)

IR(KBr)cm-1: 3301, 1639, 1522, 1457, 1314, 749, 705

[0084]

Example 15

N-(2-aminophenyl)-4-[N-(2-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 91)

mp: 191-194 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 2.53(3H, s), 4.53(2H,d, 5.9), 4.88(2H,br.s), 6.60(1H, dd, 6.6, 8.1), 6.78(1H, d, 7.3), 6.97(1H, dd, 7.3, 8.1), 7.17(1H, d, 7.3), 7.29(1H, dd, 5.1, 8.1), 7.47(2H, d, 8.1), 7.77(1H, dd, 1.5, 8.1), 7.97(2H, d, 8.1), 8.51(1H, dd, 1.5, 5.1), 9.06(1H, t, 5.9), 9.64(1H, s)

IR(KBr)cm-1: 3261, 1642, 1523, 1310, 753

[0085]

Example 16

N-(2-aminophenyl)-4-[N-(6-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 93)

mp: 186-190 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.36(3H, s), 4.56(2H, d, 5.9), 4.88(2H, s), 6.60(1H, dd, 7.4, 7.8), 6.78(1H, d, 7.8), 6.97(1H, dd, 6.9, 6.9), 7.16(1H, d, 7.4), 7.37(1H, d, 8.3), 7.45(2H, d, 8.3), 7.95(2H, d, 8.3), 8.13(1H, dd, 2.0, 8.3), 8.96(1H, s), 9.24(1H, t, 5.9), 9.63(1H, br.s)

IR(KBr)cm-1: 3302, 1636, 1602, 1523, 1489, 1457, 1313, 751

[0086]

Example 17

N-(2-aminophenyl)-4-[N-(2-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 105)

mp: 176-178 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.54(2H, t, 5.9), 4.90(2H, br.s), 6.60(1H,

ddd, 1.5, 7.3, 7.3), 6.78(1H, d, 8.1), 6.97(1H, ddd, 1.5, 7.3, 7.3), 7.18(1H, d, 8.1), 7.48-7.54(3H, m), 7.94-7.99(3H, m), 8.49(1H, dd, 2.1, 5.1), 9.23(1H, br.t, 5.9), 9.65(1H, br.s)

IR(KBr)cm-1: 3264, 1649, 1524, 1400, 1309, 751

[0087]

Example 18

N-(2-aminophenyl)-4-[N-(6-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 107)

mp: 205-208 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 5.57(2H, d, 5.9), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 8.1), 6.96(1H, dd, 7.3, 8.1), 7.16(1H, d, 8.1), 7.45(2H, d, 8.1), 7.66(1H, d, 8.8), 7.95(2H, d, 8.1), 8.27-32(1H, m), 8.90(1H, d, 2.1), 9.38(1H, t, 5.9), 9.63(1H, s)

IR(KBr)cm-1: 3318(br.), 2929, 1646, 1590, 1525, 1503, 1454, 1108, 745

[0088]

Example 19

N-(2-aminophenyl)-4-(N-isonicotinoylaminomethyl)benzamide (Table 1: Compound 123)

mp: 234-237 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.57(2H, t, 5.9), 4.88(2H,br.s), 6.59(1H,dd, 6.6, 7.3), 6.78(1H, d, 8.1), 6.96(1H, dd, 7.3, 7.3), 7.16(1H, d, 7.3), 7.45(2H, d, 8.1), 7.81(2H, d, 1.5, 4.4), 7.95(2H, d, 8.1), 8.75(2H, d, 6.6), 9.41(1H, t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3298, 1646, 1550, 1525, 1457, 1304, 843, 760, 695

[0089]

Example 20

N-(2-aminophenyl)-4-[N-(pyrazin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 131)

mp: 207 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.58(2H, d, 5.9), 4.88(2H,br.s), 6.59(1H,dd, 7.3, 7.3), 6.77(1H, d, 8.1), 6.94(1H, ddd, 1.5, 7.3, 8.1), 7.15(1H, d, 7.3), 7.45(2H, d, 8.1), 7.93(2H, d, 8.1), 8.77(1H, d, 1.5), 8.90(1H, d, 2.1), 9.21(1H, s), 9.55-9.61(2H, m)

IR(KBr)cm-1: 3368(br.), 1657, 1524, 1455, 1295, 1023, 751

[0090]

Example 21

N-(2-aminophenyl)-4-[N-(thiophen-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 134)

mp: 202-205 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.52(2H, t, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 6.6, 7.3), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.15-7.18(2H, m), 7.43(2H,d, 8.1), 7.78(1H, d, 4.4), 7.82(1H, d, 3.7), 7.95(2H, d, 8.1), 9.12(1H, br.t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3306, 1633, 1523, 1456, 1297, 750, 716

[0091]

Example 22

N-(2-aminophenyl)-4-(N-furoylaminomethyl)benzamide (Table 1: Compound 137)

mp: 197 ℃(dec.)

1H NMR(270MHz. DMSO-d6) δ ppm: 4.59(2H, d, 6.6), 4.86(2H,br.s), 6.59(1H, t, 6.6), 6.63(1H, dd, 1.5, 3.6), 6.78(1H, d, 8.1), 6.96(1H, dd, 7.3, 6.6), 7.10-7.20(2H, m), 7.41(2H, d, 8.1), 7.84(1H, s), 7.94(2H, d, 8.1), 9.00(1H, br.t, 5.9), 9.62(1H, s)

IR(KBr)cm-1: 3245, 1651, 1573, 1545, 1323, 1241, 745

[0092]

Example 23

N-(2-aminophenyl)-4-[N-(pyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 139)

mp: 216-220 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 4.50(2H, d, 5.9), 4.88(2H,br.s), 6.10(1H,dd, 2.1, 5.9), 6.59(1H, dd, 7.3, 7.3), 6.77(1H, dd, 1.5, 8.1), 6.84-6.88(2H, m), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 7.3), 7.41(2H, d, 8.1), 7.94(2H, d, 8.1), 8.62(1H, br.t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3275, 1655, 1584, 1534, 1458, 1316, 747

[0093]

Example 24

N-(2-aminophenyl)-4-[N-(N'-methylpyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 140)

mp: 177-179 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(3H, s), 4.46(2H, d, 5.9), 4.88(2H, d, 5.9), 6.03(1H, dd, 2.1, 4.4), 6.59(1H, dd, 8.1, 8.1), 6.77(1H, d, 8.1), 6.84-6.97(2H, m), 7.16(1H, d, 7.3), 7.41(2H, d, 8.1), 7.93(2H, d, 8.1), 8.61(1H, t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3325(br.), 1630, 1551, 1520, 1507, 1324, 1265, 1154, 740

[0094]

Example 25

N-(2-aminophenyl)-4-[N-(isoxazol-5-carbonyl)aminomethyl]benzamide (Table 1: Compound 143)

mp: 183-185 ℃(dec.)

1H NMR(270 MHz. DMSO-d6) δ ppm: 4.53(2H, d, 6.6), 4.89(2H, br.s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 7.3), 6.97(1H, dd, 7.3, 8.1), 7.12(1H, d, 2.1), 7.16(1H, d, 8.1), 7.44(2H, d, 8.1), 7.95(2H, d, 8.1), 8.76(1H, d, 1.5), 9.61(1H, t, 5.9), 9.64(1H, br.s)

IR(KBr)cm-1: 3278(br.), 1636, 1576, 1522, 1458, 1220, 749

[0095]

Example 26

N-(2-aminophenyl)-4-[N-(3-methylisothiazol-5-carbonyl)aminomethyl] benzamide (Table 1: Compound 144)

mp: 168-169 ℃.

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.47(3H, s), 4.54(2H, d, 5.9), 4.89(2H, br.s), 6.60(1H,dd, 7.3, 7.3), 6.78(1H, d, 7.3), 6.97(1H, ddd, 1.0, 7.3, 8.1), 7.17(1H, d, 7.3), 7.44(2H, d, 8.1), 7.73(1H, s), 7.96(2H, d, 8.1), 9.44(1H, t, 5.9), 9.64(1H, br.s)

IR(KBr)cm-1: 3310, 1637, 1503, 1294, 751

[0096]

Example 27

N-(2-aminophenyl)-4-[N-(imidazol-4-carbonyl)aminomethyl]benzamid e (Table 1: Compound 145)

mp: (amorphous).

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.49(2H, d, 6.4), 4.87(2H, br.s), 6.59(1H, dd, 6.9, 6.9), 6.77(1H, d, 6.9), 6.96(1H, dd, 7.4, 7.4), 7.16(1H, d, 6.9), 7.41(2H,d, 6.9), 7.64(1H, br. s), 7.73(1H, br.s), 7.92(2H, d, 6.9), 8.56(1H, br.t, 6.4), 9.61(1H,

s), 12.5(1H, br.s)

IR(KBr)cm-1: 3278(br.), 1636, 1576, 1522, 1458, 1220,749

[0097]

Example 28

N-(2-aminophenyl)-4-[N-(3-aminophenyl)acetylaminomethyl]benzamide (Table 1: Compound 23)

mp: 171-176 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.34(2H, d, J=5.9 Hz), 5.24(4H, br.s), 6.48-6.63(4H, m), 6.78-6.81(1H, m), 6.94-7.00(2H, m), 7.18(1H, d, J=8.1 Hz), 7.34(2H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz), 8.50(1H, t, J=5.9 Hz), 9.61(1H, s)

[0098]

Example 29

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)acetylaminomethyl]benzamide (Table 1: Compound 74)

mp: 127 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(2H, s), 4.40(2H, d, J=5.88), 7.15-7.29(3H, m), 7.37(1H, d, J=6.62), 7.43(2H, d, J=8.80), 7.96(1H, m), 7.98(2H, d, J=8.80), 8.40(1H, d, J=8.80), 8.79-8.87(3H, m), 10.20(1H, s)

[0099]

Example 30

N-(2-aminophenyl)-4-[3-(pyridin-3-yl)propionamido]benzamide (Table 1: Compound 75)

mp: 183-186 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.51(2H, t, 7.3), 2.88(2H, d, 7.3), 4.31(2H, d, 5.9), 4.89(2H, br.s), 6.60(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 8.1), 7.23(2H, d, 8.8), 7.28-7.33(1H, m), 7.63(1H, d, 8.1), 7.89(2H, d, 8.1), 8.41-8.45(3H, m), 9.62(1H, br.s)

IR(KBr)cm-1: 3407, 3313, 1640, 1552, 1522, 1456, 1309, 746, 717

[0100]

Example 31

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetyl aminomethyl]benzamide (Table 1: Compound 61)

(31-1) To a suspension of 0.22 g of sodium hydride (5.5 mmol) in DMF (2 ml) was added dropwise a solution of 0.48 g of 3-hydroxypyridine (5.0mmol)

in DMF (2 ml) at room temperature, and the mixture was stirred for an hour. The resulting brown solution was ice-cooled, 0.81 ml of tert-butyl bromoacetate (5.5 mmol) was added, and the mixture was stirred under ice-cooling for an hour followed by stirring at room temperature for 2 hours. After addition of water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform: ethyl acetate = 5:1), to give 0.34 g of tert-butyl 3-pyridyloxyacetate (Yield: 32.5 %) as a clear oil.

1H NMR (CDCl3) δ ppm: 1.49(9H, s), 4.56(2H, s), 7.18-7.24(2H, m), 8.26(1H, dd, J=1.5, 3.6 Hz), 8.32(1H, d, J=2.9)

[0101]

(31-2) To a solution of 0.14 g of the compound from the process (31-1) (0.67 mmol) in dichloromethane (2 ml) was added 2 ml of trifluoroacetic acid, and the solution was stirred at room temperature for 3 hours. After evaporation, diisopropyl ether was added, and the precipitated solid was collected by filtration and dried to give 0.15 g of 3-pyridyloxyacetic acid trifluoroacetate (Yield: 83.8 %) as a light yellow solid.

1H NMR(DMSO-d6) δ ppm: 4.86(2H, s), 7.57(1H, dd, J=4.4, 8.1 Hz), 7.67(1H, ddd, J=1.5, 1.5, 8.8 Hz), 8.31(1H, d, J=5.1 Hz), 8.46(1H, d, J=2.1 Hz), 13(1H, br.s)

[0102]

(31-3) To a suspension of 100 mg of the compound from the process (31-2) (0.37 mmol) and 255 mg of the compound from Example 1, the process (1-4) (0.75 mmol) in dichloromethane (5 ml) was added 0.14 ml of triethylamine (1.0 mmol), and the mixture was cooled with ice. Under ice-cooling, to the mixture was added a solution of 140 mg of 2-chloro-N,N'-dimethylimidazolinium chloride (0.83 mmol) in dichloromethane (6 ml), and the mixture was warmed to room temperature with stirring for 7 hours, and left at room temperature overnight. After adding water and saturated brine, the mixture was extracted with chloroform.

[0103]

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel

(eluent: ethyl acetate:methanol = 10:1) to give 0.37 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)oxyacetylamino methyl]benzamide (Yield: quantitative) as a clear oil.
1H NMR(CDCl3) δ ppm: 1.52(9H, 5), 4.62(2H, s), 4.63(2H, d, J=7.3 Hz), 6.76(1H, br.s), 6.9-7.0(1H, br.s), 7.15-7.35(5H, m), 7.40(2H, d, J=8.1 Hz), 7.82(1H, d, J=8.1 Hz), 7.95(2H, d, J=8.1 Hz), 8.32(1H, dd, J=2.1, 4.4 Hz), 8.37(1H, d, J=2.8 Hz), 9.20(1H, br.s)
[0104]

(31-4) To a solution of 175 mg of the compound from the process (31-3) (0.37 mmol) in dioxane (2 ml) and methanol (2 ml) was added 4N hydrochloric acid-dioxane (2 ml), and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 90 mg of N-(2-aminophenyl)-4-[N-(pyridyl-3-yl) oxyacetylaminomethyl]benzamide (Yield: 64.6 %) as an opalescent solid.
1H NMR(DMSO-d6) δ ppm: 4.42(2H, d, J=5.9 Hz), 4.69(2H, s), 4.89(2H, br.s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.33-7.39(4H, m), 7.92(2H, d, J=8.1 Hz), 8.21(1H, dd, J=1.5, 4.4 Hz), 8.35(1H, d, J=2.9 Hz), 8.80(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)
IR(KBr)cm: 3307, 1672, 1631, 1523, 1456, 1429, 1269, 1231, 803, 1756
[0105]

Example 32

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxycarbonyl] aminomethylbenzamide (Table 1: Compound 82)

(32-1) To a solution of 384 mg of 3-pyridylmethanol (3.52 mmol) in 5 ml of dry THF were added 523 mg of N,N'-carbonyldiimidazole (3.22 mmol) at room temperature. After stirring for an hour, to the mixture was added 1.0 g of the compound from Example 1, the process (1-4) (2.93 mmol) in 6 ml of dry THF.
[0106]

After being left at room temperature overnight, to the mixture was added 100 ml of chloroform, and the mixture was washed with water (3 x 20

ml) and saturated brine, and dried out with anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent:chloroform:methanol = 30:1) to give 1.27 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methoxycarbonyl]aminomethylbenzamide (Yield: quantitative) as an amorphous solid.

1H NMR (270 MHz, CDCl3) δppm:1.51(9H,s), 4.45(2H, d, J=5.9 Hz), 5.16(1H, s), 7.1-7.5(7H, m), 7.70(1H, d, J=8.1 Hz), 7.80(1H, d, J=7.3 Hz), 7.93(1H, d, J=8.1 Hz), 8.57(1H, d, J=4.4 Hz), 8.63(1H, s), 9.17(1H, s).

[0107]

(32-2) The compound from the process (32-1)(1.2 g, 2.8 mmol) was dissolved in 10 ml of methanol. To the solution was added 20 ml of 4N-hydrochloric acid-dioxane. The mixture was stirred at room temperature for 1.5 hours, and then poured into diluted sodium hydroxide aq. and extracted with chloroform (3 x 60 ml). The combined organic layer was washed twice with saturated brine, dried out with anhydrous magnesium sulfate and concentrated to give 0.88 g of crystals, which were then recrystallized from 16 ml of ethanol, to give 668 mg of N-(2-aminophenyl)-4-[(pyridin-3-yl) methoxycarbonyl]aminomethylbenzamide (Yield: 73 %).

[0108]

mp: 159-160 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.28(2H, d, J=5.9 Hz), 4.86(2H, s), 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=7 Hz), 6.97(1H, t, J=7 Hz), 7.17(1H, d, J=8 Hz), 7.3-7.5(3H, m), 7.78(1H, d, J=8 Hz), 7.93(2H, d, J=8 Hz), 8.53(1H, d, J=3.7 Hz), 8.59(1H, s), 9.61(1H, s).

IR(KBr)cm-1: 3295, 1648, 1541, 1508, 1457, 1309, 1183, 742

As described in Example 32, the compounds of Examples 33 to 53 were prepared, each of whose melting point (mp), 1H NMR data, IR data are shown below.

[0109]

Example 33

N-(2-aminophenyl)-4-(benzyloxycarbonyl)aminomethylbenzamide (Table 1: Compound 11)

mp: 174-178 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.28(2H, d, 5.9), 4.89(2H, br.s), 5.06(2H, s), 6.59(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.3-7.4(6H, m), 7.93(3H, m), 9.63(1H, s).

IR(KBr)cm-1: 3332, 1687, 1652, 1536, 1456, 1279, 747

[0110]

Example 34

N-(2-aminophenyl)-4-[(4-(imidazol-1-yl)benzyl)oxycarbonyl]aminomethylbenzamide (Table 1: Compound 47)

mp: 195-198 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.29(2H, d, J=6.6 Hz), 4.88(2H, s), 5.10(2H, s), 6.60-6.63(1H, m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.11(1H, s), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.1 Hz), 7.49(2H, d, J=8.8 Hz), 7.66(2H, d, J=8.1 Hz), 7.74(1H, s), 7.92-7.96(3H, m), 8.25(1H, s), 9.62(1H, s)

[0111]

Example 35

N-(2-aminophenyl)-4-[(pyridin-2-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 51)

mp: 166-167 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.30(2H, d, 5.9), 4.88(2H, br.s), 5.12(2H, s), 6.60(1H, dd, 7.3, 8.1) , 6.78(1H, d, 8.1), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 7.3), 7.33(1H, dd, 3.7, 7.3), 7.40(3H, d, 8.1), 7.83(1H, ddd, 1.5, 7.3, 8.1), 7.94(2H, d, 8.1), 8.03(1H, t, 5.9), 8.55(1H, d, 5.1), 9.62(1H, br.s)

IR(KBr)cm-1: 3334, 1694, 1632, 158, 1276, 755

[0112]

Example 36

N-(2-aminophenyl)-4-[2-(pyridin-2-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 52)

mp: 146-148 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.04(2H, t, 6.6), 4.23(2H, d, 5.9), 4.36(2H, t, 6.6), 4.88(2H, br.s), 6.60(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.15-7.30(3H, m), 7.34(2H, d, 8.1), 7.69 -7.77(2H, m), 7.92(2H, d, 7.3), 8.50(1H, d, 4.4), 9.62(1H, br.s)

IR(KBr)cm-1: 3330, 1690, 1633, 1594, 1524, 1277, 760

[0113]

Example 37

N-(2-aminophenyl)-4-[(6-methylpyridin-2-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 59)

mp: 138 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.47(3H, s), 4.30(2H, d, J=5.9), 5.07(4H, s), 6.63(1H, t, J=8.1), 6.80 (1H, d, J= 7.34), 6.98(1H, t, J=8.1), 7.18(3H, d, J=7.3), 7.40(2H, d, J=8.1), 7.71(1H, t, J=8.1), 7.94(2H, d, J=8.1), 8.03(1H, t, J=5.9), 9.66(1H, s)

IR(KBr)cm-1: 1259, 1634, 1693, 3335.

[0114]

Example 38

N-(2-aminophenyl)-4-[(2-(pyridin-3-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 83)

mp: 120-125 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.91(2H, t, J=6.60), 4.22(4H, t, J=6.6), 4.89(2H, s), 6.55-6.63(1H, m), 6.78(1H, dd, J=8.1, 1.5), 6.97(1H, t, J=6.6), 7.17(1H, d, J=6.6), 7.33(3H, d, J=8.1), 7.69(1H, d, J=8.1), 7.79(1H, t, J=6.6), 7.93(2H, d, J=8.0), 8.43-8.49(2H, m), 9.62(1H, s)

IR(KBr)cm-1: 1260, 1655, 1705, 3234

[0115]

Example 39

N-(2-aminophenyl)-4-[3-(pyridin-3-yl)propyloxycarbonyl]aminomethyl benzamide (Table 1: Compound 84)

mp: 121-124 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.83-1.94(2H, m), 2.67(2H, t, 7.3), 3.98(2H, t, 6.6), 4.26(2H, d, 5.9), 4.89(2H, br.s), 6.60(1H, dd, 8.1, 8.1), 6.78(1H, d, 7.3), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 8.1), 7.29-7.33(1H,m), 7.37(1H, d, 8.1), 7.64(1H, d, 8.1), 7.81(1H, dd, 5.9, 6.6), 7.94(2H,d, 8.1), 8.40-8.44(2H,m), 9.63(1H, br.s)

IR(KBr)cm-1: 3348, 1696, 1635, 1523, 1458, 1302, 1272, 1141, 1019, 754, 713

[0116]

Example 40

N-(2-aminophenyl)-4-[(2-methylpyridin-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 92)

mp: 164-165 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.49(3H, s), 4.28(2H,d, J=6.6), 4.89(2H, s), 5.10(2H, s), 6.60(1H, t, J=6.6), 6.78(1H, d, J=8.1), 6.9(1H, t, J=7.3), 7.17(1H, d, J=7.3), 7.21-7.26(1H, m), 7.37(2H, d, J=8.1), 7.68(1H, d, J=6.6), 7.92-8.00(3H, m), 8.39(1H, d, J=4.4), 9.62(1H, s)

IR(KBr)cm-1: 1260, 1630, 1719, 3332

[0117]

Example 41

N-(2-aminophenyl)-4-[(6-methylpyridin-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 94)

mp: 164-165 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.46(3H, s), 4.27(2H, d, J=6.6), 4.88(2H, s), 5.05(2H, s), 6.59(1H, dt, J=8.1, 1.5), 6.78(1H, dd, J=8.1, 1.5), 6.97(1H, dt, J=7.3, 1.5), 7.17(1H, d, J=7.3), 7.26(1H, d, J=8.1), 7.36(2H, d, J=8.1), 7.67(1H, dd, J=8.1, 2.2), 7.93(3H, d, J=8.1), 8.45(1H, d, J=1.5), 9.62(1H, s)

IR(KBr)cm-1: 1260, 1632, 1701, 3293

[0118]

Example 42

N-(2-aminophenyl)-4-[(2-chloropyridin-3-yl)methoxycarbonyl]aminom ethylbenzamide (Table 1: Compound 106)

mp: 159-169 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.30(2H, d, J=5.9), 5.00(2H, s), 5.13(2H, s), 6.61(1H, t, J=7.34), 6.79(1H, dd, J=8.1, 1.5), 6.98(1H, dt, J=7.3, 1.5), 7.17(1H, d, J=6.6), 7.39(2H, d, J=8.8), 7.47-7.52(1H, m), 7.91-7.96(3H, m), 8.08(1H, t, J=5.9), 8.40(1H, dd, J=4.4, 1.5), 9.64(1H, s)

IR(KBr)cm-1: 1273, 1632, 1702, 3340

[0119]

Example 43

N-(2-aminophenyl)-4-[(6-chloropyridin-3-yl)methoxycarbonyl]aminom ethylbenzamide (Table 1: Compound 108)

mp: 180-185 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.24(2H, d, J=5.9), 4.89(2H, br.s) , 5.10(2H, s), 6.60(1H, t, J=7.3), 6.78(1H, d, J=8.1), 6.97(1H, dt, J=8.1, 1.5), 7.16(1H, d, J=6.6), 7.37(2H, d, J=8.1), 7.56(1H, d, J=8.1), 7.85-8.02(4H, m),

8.44(1H, d, J=2.2), 9.62(1H, s)

IR(KBr)cm-1: 1271, 1533, 1696, 3282, 3346

[0120]

Example 44

N-(2-aminophenyl)-4-[(pyridin-4-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 121)

mp: 180-183 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.30(2H, d, 6.6), 4.89(2H, s), 5.12(2H, s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, dd, 1.5, 7.3), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 7.3), 7.34(2H, d, 5.9), 7.39(2H, d, 8.1), 7.94(2H, d, 8.1), 8.09(1H, t, 5.9), 8.57(1H, d), 9.64(1H, br.s)

IR(KBr)cm-1: 3394, 3290, 1711, 1645, 1624, 1535, 1504, 1321, 1251, 1138, 1049, 763

[0121]

Example 45

N-(2-aminophenyl)-4-[2-(thiophen-3-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 136)

mp: 128-138 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 2.90(2H, t, J=7.3), 4.17-4.26(4H, m), 4.89(2H, s), 6.60(1H, t, J=8.1), 6.78(1H, d, J=6.6), 6.97(1H, t, J=7.3), 7.06(1H, d, J=5.1), 7.17(1H, d, J=7.3), 7.26(1H, s), 7.36(2H, d, J=8.1), 7.47(1H, t, J=2.2), 7.81(1H, t, J=5.9), 7.93(2H, d, J=8.1), 9.63(1H, s).

IR(KBr)cm-1: 1252, 1638, 1716, 3314

[0122]

Example 46

N-(2-aminophenyl)-4-[(3-phenyloxazol-5-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 141)

mp: 192-195 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.30(2H, d, J=5.9), 4.89(2H, s), 5.25(2H, s), 6.60(1H, t, J=6.6), 6.68(1H, d, J=8.1), 6.94(1H, t, J=7.3), 7.09(1H, s), 7.16(1H, d, J=7.3), 7.39(2H, d, J=8.1), 7.51(4H, d, J=2.2), 7.87-7.96(5H, m), 8.12(1H, t, J=5.9), 9.63(1H, s)

IR(KBr)cm-1: 1262, 1630, 1718, 3292

[0123]

Example 47

N-(2-aminophenyl)-4-[(thiazol-5-yl)methoxycarbonyl]aminomethylben zamide (Table 1: Compound 147)

mp: 168-175 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.28(2H, d, 5.9), 4.91(2H, br.s), 5.30(2H, s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.36(2H, d, 8.1), 7.91-8.00(4H, m), 9.09(1H, s), 9.63(1H, s)

IR(KBr)cm-1: 3346(br.), 1697, 1636, 1525, 1456, 1271, 873, 753

[0124]

Example 48

N-(2-aminophenyl)-4-[2-(4-methylthiazol-5-yl)ethoxycarbonyl]aminom ethylbenzamide (Table 1: Compound 148)

mp: 130-133 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.32(3H, s), 3.07(2H, t, J=5.9), 4.15(2H, t, J=5.9), 4.25(2H, d, J=6.6), 4.89(2H, s), 6.60(1H, t, J=5.9), 6.78(1H, dd, J=7.3, 1.5), 6.97(1H, dt, J=7.3, 1.5), 7.16(1H, d, J=8.1), 7.35(2H, d, J=8.1), 7.83(1H, t, J=5.9), 7.94(2H, d, J=8.1), 8.85(1H, s), 9.62(1H, s)

IR(KBr)cm-1: 1270, 1635, 1691, 3350

[0125]

Example 49

N-(2-aminophenyl)-4-[(1-methylpiperidin-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 152)

mp: 130-135 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.49-1.78(3H, m), 1.83-2.01(3H, m), 2.30(3H, s), 2.85(2H, t), 3.74-3.94(2H, m), 4.25(2H, d, J=5.8), 6.55-6.62(3H, m), 6.78(1H, d, J=8.1), 6.97(1H, t, J=7.3), 7.16(1H, d, J=8.1), 7.37(2H, d, J=8.1), 7.79(1H, t, J=6.6), 7.93(2H, d, J=8.0), 9.66(1H, s)

IR(KBr)cm-1: 1263, 1648, 1702, 2722, 3323

[0126]

Example 50

N-(2-aminophenyl)-4-[(4-methylpiperazin-1-yl)methoxycarbonyl]amin omethylbenzamide (Table 1: Compound 153)

mp: 145-155 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.73(2H, t, J=6.6), 2.36-2.63(13H, m),

4.00(2H, t, J=6.6), 4.30(2H, d, J=5.8), 6.55-6.63(4H, m), 6.78(1H, d, J=6.6), 6.97(1H, t, J=7.3), 7.16(1H, d, J=7.3), 7.37(2H, d, J=8.7), 7.73(1H, t, J=5.9), 7.94(2H, d, J=8.0), 9.66(1H, s)

IR(KBr)cm-1: 1262, 1701, 2706, 3341

[0127]

Example 51

N-(2-aminophenyl)-4-[(tetrahydrofuran-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 155)

1H NMR(DMSO-d6) δ ppm: 1.50-1.60(1H, m), 1.88-2.00(1H, m), 2.44-2.54(1H, m), 3.41-3.47(1H, m), 3.56-3.77(3H, m), 3.85-4.04(2H, m), 4.25(2H, d, J=5.9 Hz), 4.89(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=8.1), 7.37(2H, d, J=8.1 Hz), 7.81(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.1), 9.62(1H, br.s)

IR(KBr)cm-1: 3349, 1695, 1635, 1523, 1457, 1259, 754

[0128]

Example 52

N-(2-aminophenyl)-4-(phenoxycarbonyl)aminomethylbenzamide (Table 1: Compound 12)

mp: 174-175 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.36(2H, d, 5.9), 4.90(2H,br.s), 6.60(1H,dd, 7.3, 7.3), 6.77(1H, dd, 7.3, 7.3), 6.98(1H, ddd, 1.5, 7.3, 7.3), 7.05-7.24(4H, m), 7.39-7.46(4H, m), 7.97(2H, d, 8.1), 8.41(1H, t, 5.9), 9.65(1H, br.s)

IR(KBr)cm-1: 3443, 3362, 3313, 1732, 1706, 1636, 1527, 1493, 1458, 1305, 1217, 748

[0129]

Example 53

N-(2-aminophenyl)-4-[(pyridin-3-yl)oxycarbonyl]aminomethylbenzamide (Table 1: Compound 81)

mp: 209 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.38(2H, d, 6.6), 4.90(2H, br.s) , 6.55-6.63(1H, m), 6.78(1H, d, 8.1), 7.00(1H, dd, 7.3, 7.3), 7.17(1H, d, 8.8), 7.37-7.47(3H, m), 7.64(1H, d, 8.8), 7.97(2H, d, 8.1), 8.43(2H, d, 3.1), 8.59(1H, t, 5.9), 9.66(1H, br.s)

[0130]

Example 54

N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxythiocarbonyl]aminomethylbenzamide (Table 1: Compound 86)

(54-1) To a solution of 20 mg of 3-pyridylmethanol (0.18 mmol) in 5 ml of dry THF were added 30 mg of N,N'-thiocarbonyldiimidazole (0.16 mmol) at room temperature. After stirring overnight, to the mixture were added 50 mg of the compound from Example 1, the process (1-4) (0.14 mmol).

[0131]

After leaving at room temperature overnight, to the solution was added 100 ml of chloroform, and the solution was washed with water (3 x 20 ml) and then saturated brine, and dried out with anhydrous magnesium sulfate. After evaporation, the residue was purified by column chromatography on silica gel (eluent: chloroform:methanol = 30:1) to give 70 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methoxythiocarbonyl]aminomethylbenzamide (Yield: 88 %) as amorphous.

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.45(9H, s), 4.73(2H, d, J=5.9 Hz), 5.52(2H, s), 6.73-7.33(3H, m), 7.35-7.43(2H, m), 7.58-7.95(5H, m), 8.14-8.65 (3H, m), 9.80(1H, s), 9.91(1H, t)

[0132]

(54-2) 50 mg of the compound from the process (54-1) (0.10 mmol) was dissolved in 3 ml of methanol. To the solution was added 3 ml of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 1.5 hours. The mixture was poured into diluted sodium hydroxide aq. to neutralize the residual hydrochloric acid, and then was extracted with chloroform (3 x 10 ml). The organic layer was washed twice with saturated brine, dried out with anhydrous magnesium sulfate and concentrated to give 34 mg of N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxythiocarbonyl] aminomethylbenzamide (Yield: 87 %).

mp: 154-156 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.73(2H, d, J=5.9 Hz), 4.88(2H, s), 5.52(2H, s), 6.60(1H, t, J=7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, t, J=8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.29-7.41(3H, m), 7.83-7.95(3H, m), 8.50-8.56(1H, m),

8.65(1H, s), 9.62(1H, s), 9.93(1H, t)

[0133]

Example 55

Preparation of N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl) ureidomethyl]benzamide (Table 1: Compound 88)

(55-1) To a solution of 3-picolylamine (0.28g, 2.6 mmol) in THF (10 ml) was added N,N'-carbonyldiimidazole (0.42 g, 2.4 mmol) at room temperature, and the mixture was stirred for an hour. To the solution was added the compound from Example 1, the process (1-4) (0.58 g, 1.8 mmol) at room temperature, and the solution was stirred for 3 hours and then left overnight.

[0134]

After diluting with water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol = 10:1) to give N-[2-(N-tert-butoxycarbonyl) amino]phenyl-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (0.77 g, Yield: 90 %) as a white amorphous solid.

1H NMR(270MHz, CDCl3) δ ppm: 1.46(9H, s), 4.20(2H, d, 5.1), 4.28(2H, d, 4.3),6.1-6.3(2H, m), 7.0-7.25(4H, m), 7.33(1H, d, 7.3), 7.49-7.54(2H, m), 7.58-7.64(3H, m), 7.75(1H, s), 8.28(1H, br.s), 8.39(1H, d, 5.1), 9.65 (1H, br.s)

[0135]

(55-2) To a solution of the compound from the process (55-1)(0.63 g, 1.32 mmol) in dioxane (4 ml) and methanol (2 ml) was added 4N hydrochloride-dioxane (4 ml), and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate-methyl ethyl ketone. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether to give N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (0.37 g, Yield: 74.7 %) as a brown solid.

[0136]

mp: 167-175 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.27(2H, d, 5.9), 4.31(2H, d, 5.9), 4.89(2H, br.s), 6.57-6.63(3H, m), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1),

7.17(1H, d, 7.3), 7.32-7.38(3H, m), 7.66(1H, d, 8.1), 7.93(2H, d, 8.1), 8.44(1H, d, 5.1), 8.49(1H, d, 2.1), 9.63(1H, br.s)

IR(KBr)cm-1: 3344, 3241, 1645, 1560, 1527, 1505, 1283, 751, 708

[0137]

As described in Example 55, the compounds of Examples 56 to 59 were prepared, each of whose melting point (mp), 1H NMR data, IR data are shown below.

Example 56

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)ureidomethyl]benzamide

(Table 1: Compound 24)

mp: 206-208 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 4.35(2H, d,J=5.9 Hz), 4.93(4H, br.s), 6.13(1H, d, J=7.3 Hz), 6.51-6.62(3H, m), 6.74-6.98(3H, m), 7.12-7.18(1H, m), 7.41(2H,d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.28(1H, s), 9.61(1H, s)

[0138]

Example 57

N-(2-aminophenyl)-4-[N'-(pyridin-3-yl)ureidomethyl]benzamide (Table 1: Compound 87)

mp: 187-190 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.39(2H, d, 5.9), 4.89(2H,br.s), 6.59(1H, d, 7.3, 7.3), 6.77(1H, d, 6.6), 6.88(1H, t, 5.9), 6.97(1H, ddd, 1.5, 6.6, 7.3 Hz), 7.16(1H, d, 8.1), 7.26(1H, dd, 4.4, 8.1), 7.42(2H, d, 8.8), 7.95(2H, d, 8.1), 7.89-7.96(1H, m), 8.12(1H, dd, 1.5, 4.4), 8.56(1H, d, 3.0), 8.85(1H, s), 9.62(1H, s)

IR(KBr)cm-1: 3248, 1663, 1541, 1423, 1280, 1054

[0139]

Example 58

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)thioureidomethyl]benzamide

(Table 1: Compound 25)

mp: 123 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 4.80(2H, d, J=5.1 Hz), 4.87(2H, s), 5.12(2H, s), 6.36(1H, dd, J=1.5, 8.1 Hz). 6.48-6.63(3H, m), 6.78(1H, d, J=6.6 Hz), 6.94-7.00(2H, m), 7.17(1H, d, J=8.1 Hz), 7.42(2H, d, J=8.1 Hz), 7.92-8.01(3H, m), 9.46(1H, s), 9.61(1H, s)

[0140]

Example 59

N-(2-aminophenyl)-4-[N'-(3-nitrophenyl)thioureidomethyl]benzamide (Table 1: Compound 20)

mp: 160 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.87(2H, d, J=5.1 Hz), 7.27-7.33(3H, m), 7.46-7.63(5H, m), 7.89-7.95(2H, m), 8.05(2H, d, J=8.1 Hz), 8.70(1H,s), 8.84(1H, t, J=8.9 Hz), 10.37 (1H, s)

[0141]

Example 60

Preparation of N-(2-aminophenyl)-4-[2-(N-(pyridin-3-ylacetyl)amino) ethyl]benzamide (Table 1: Compound 77)

(60-1) To a suspension of 3.40 g of terephthalaldehydic acid (22.6 mmol) in toluene (25 ml) was added thionyl chloride (4 ml), and the mixture was heated with stirring at for 2 hours. After cooling and evaporation, the residue was dissolved in THF (50 ml) to give a solution of the acid chloride. To a solution of 4.16 g of the compound from Example 1, the process (1-2) (20.0 mmol) in THF (10 ml) was added triethylamine (6 ml, 42.8 mmol) and then the above solution of the acid chloride was added dropwise under ice-cooling for 30 min.

[0142]

After stirring for 5 hours, to the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (gradient elution with chloroform to chloroform:ethyl acetate = 10:1) to give 3.42 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-formylbenzamide (Yield: 50.2 %) as a light brown solid.

1H NMR(CDCl3) δ ppm: 1.52(9H, s), 6.77(1H, br.s), 7.16-7.18(2H, m), 7.23-7.26(1H, m), 7.88(1H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 8.13(2H, d, J=8.8 Hz), 9.57(1H, br.s), 10.11(1H, br.s)

IR(KBr)cm-1: 3326, 3251, 1707, 1696, 1659, 1603, 1165

[0143]

(60-2) A suspension of 3.0 g of the compound from the process (60-1)

(8.82 mmol) and 4.5 g of ethoxycarbonylmethyl triphenylphosphine (12.9 mmol) in toluene (10 ml) was stirred in a stream of nitrogen at 80 ℃ for 5.5 hours. After cooling, the mixture was diluted with ethyl acetate; washed with saturated sodium bicarbonate aq., water and saturated brine, and dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate = 20:1) to give 3.3 g of ethyl 4-(N-2-(N-tert-butoxycarbonyl)aminophenyl)aminocarbonylcinnamate (Yield: 91.1 %) as a yellow amorphous solid.

1H NMR(CDCl3) δppm: 1.35(3H, t, J=7.3 Hz), 1.52(9H, s), 4.28(2H, q, J=7.3 Hz), 6.52(1H, d, J=15.1 Hz), 6.80(1H, br.s), 7.16-7.25(3H, m), 7.61(2H, d, J=8.1 Hz), 7.71(1H, d, J=15.1 Hz), 7.82(1H, d, 7.3), 7.98(2H, d, J=8.1 Hz), 9.34 (1H, br.s)

[0144]

(60-3) To a solution of 2.50 g of the compound from the process (60-2) (6.09 mmol) in THF (30 ml) and methanol (40 ml) was added 10 % Pd/C (wet, 0.5 g) in a stream of nitrogen, and then stirred in a stream of hydrogen for 30 min. After filling with nitrogen, the mixture was filtered to remove the catalyst, and the filtrate was evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 2.23 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(2-ethoxycarbonyl)ethylbenzamide (Yield: 88.8 %) as a white solid.

1H NMR(CDCl3) δppm: 1.25(3H, t, J=7.3 Hz), 1.52(9H, s), 2.65(2H, t, J=7.3 Hz), 3.02(2H, t, J=7.3 Hz), 4.13(2H, q, J=7.3 Hz), 6.77(1H, br.s), 7.16-7.33(5H, m), 7.78(1H, d, J=8.1 Hz), 7.89(2H, d, J=8.8 Hz), 9.06(1H, br.s)

[0145]

(60-4) To a suspension of 2.21 g of the compound from the process (60-3) (5.36 mmol) in methanol (10 ml) and water (15 ml) was added 0.37 g of lithium hydroxide monohydrate (8.82 mmol), and the mixture was stirred at 40 ℃ for 3 hours. After cooling, to the mixture was added 10 % hydrochloric acid and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diisopropyl ether, and the precipitated solid was filtered and dried to give 1.87 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(2-carboxyethyl)benzamide (Yield: 90.8 %) as a white solid.

1H NMR(DMSO-d6) δppm: 1.45(9H, s), 2.59(2H, t, J=7.3 Hz), 2.91(2H, t, J=7.3 Hz), 7.13-7.20(2H, m), 7.40(2H, d, J=8.1 Hz), 7.54(2H, dd, J=7.3, 2.1), 7.88(2H, d, J=8.1 Hz), 8.66(1H, br.s), 8.66(1H, br.s), 9.79(1H, br.s)

[0146]

(60-5) To a suspension of 0.12 g of the compound from the process (60-4) (0.3 mmol) in benzene (5 ml) were added 0.1 ml of triethylamine (0.7 mmol) and 0.3 g of molecular sieves 4A, and the mixture was stirred in a stream of nitrogen for 0.5 hours. To the mixture was added 0.15 ml of diphenylphosphoryl azide (0.7 mmol), and the mixture was refluxed with heating for 2 hours. After cooling, to the mixture was added 0.4 ml of benzyl alcohol (3.8 mmol), and the mixture was refluxed with heating for additional 2.5 hours. After diluting with ethyl acetate, the reaction mixture was washed with water and saturated brine.

[0147]

The organic layer was dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate = 4:1) to give 129 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl] -4-(N-benzyloxycarbonyl)aminoethylbenzamide (Yield: 88 %) as a clear oil.

1H NMR(CDCl3) δppm: 1.51(9H, s), 2.89(2H, t, J=7.3 Hz), 3.45-3.54(2H, m), 4.8(1H, m), 5.10(2H, s),6.76(1H, br.s), 7.20-7.38(10H, m), 7.79(1H, d, J=8.8 Hz), 7.89(2H, d, J=8.1 Hz), 9.10(1H, br.s)

[0148]

(60-6) To a solution of 129 mg of the compound from the process (60-5) (0.26 mmol) in methanol (10 ml) was added 10 % Pd/C (wet, 0.05 g) in a stream of nitrogen, and then stirred in a hydrogen stream for 2 hours. After removing the catalyst, the filtrate was evaporated and dried. The residue was dissolved in dichloromethane (5ml). To the solution were added 0.18 g of 3-pyridineacetic acid hydrochloride (1.04 mmol) and then 0.28 g of triethylamine (2.0 mmol), and the mixture was ice-cooled. Under ice-cooling, to the mixture was added 0.17 g of 2-chloro-N,N'-dimethylimidazolinium chloride (1.0 mmol), and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated.The residue was purified by column chromatography on silica

gel (eluent: ethyl acetate:methanol = 10:1) to give 50 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-(N-(pyridin-3-ylacetyl)amino) ethyl]benzamide (Yield: 40 %) as a colorless oil.

[0149]

1H NMR (CDCl3) δ ppm: 1.48(9H, s), 2.80(2H, t, J=6.6 Hz), 3.42(2H, m), 3.52(2H, s), 6.33(1H, t-like, J=5.9 Hz), 7.09(2H, d, J=8.1 Hz), 7.14-7.20(2H, m), 7.24(1H, dd, J=4.4, 7.3Hz), 7.41(1H, dd, J=3.7, 5.9 Hz), 7.50(1H, s), 7.58(1H, dd, J=1.5, 5.9 Hz), 7.69(1H, dd, J=3.7, 5.9Hz), 7.75(2H, d, J=8.1 Hz), 8.22(1H, d, J=2.1 Hz), 8.44(1H, dd, J=1.5, 4.4 Hz), 9.49(1H, br.s)

[0150]

(60-7) To a solution of 50 mg of the compound from the process (60-6) (0.10 mmol) in dioxane (2 ml) and methanol (1 ml) was added 4N hydrochloric acid-dioxane (2 ml), and the mixture was stirred at room temperature for 2.5 hours. To the mixture was added saturated sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was dried to give 22 mg of N-(2-aminophenyl)-4-[2-(N-(pyridin-3-ylacetyl)amino)ethyl]benzamide (Yield: 59 %) as an amorphous solid.

[0151]

1H NMR(DMSO-d6) δ ppm: 2.7-2.9(4H, m), 3.42(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7. 16(1H, d, J=7.3 Hz), 7.29-7.32(3H, m), 7.59(1H, d, J=8.1 Hz), 7.89(1H, d, J=8.1 Hz), 8.22(1H, t-like), 8.41-8.43(2H, m), 9.62(1H, br.s)

[0152]

Example 61

Preparation of N-(2-aminophenyl)-4-[2-(N-(3-picolyl)aminocarbonyl) ethyl]benzamide (Table 1: Compound 80)

(61-1) To a suspension of 0.58 g of the compound from Example 60, the process (60-4) (1.5 mmol) in dichloromethane (5 ml) were added 0.22 g of 3-picolylamine (2.0 mmol) and 0.56 ml of triethylamine (4.0 mmol). Under ice-cooling, to the mixture was added 0.39 g of 2-chloro-N,N'-dimethylimidazolinium chloride (2.0 mmol) in dichloromethane (5 ml), and the mixture was stirred for 1.5 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

[0153]

The organic layer was washed with water and saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:methanol:NH_3 aq. = 100:10:1) to give 0.71 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-(N-(3-picolyl)aminocarbonyl)ethyl]benzamide (Yield: 94 %) as a light brown oil.

1H NMR(CDCl3) δppm: 1.45(9H, s), 2.42(2H, t, J=7.3 Hz), 2.98(2H, t, J=7.3 Hz), 4.32(2H, d, J=6.6 Hz), 6.44(1H, t, J=6.6 Hz), 7.14-7.27(5H, m), 7.48-7.57(3H, m), 7.63-7.68(3H, m), 7.90(1H, d, J=2.1 Hz), 8.43(1H, dd, J=1.4, 4.4 Hz), 9.86(1H, br.s)

[0154]

(61-2) To a solution of 0.70 g of the compound from the process (61-1) (1.47 mmol) in dioxane (5 ml) was added 4N hydrochloride-dioxane (5 ml) and then methanol (2 ml), and the mixture was stirred at room temperature for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.42 g of N-(2-aminophenyl)-4-[2-(N-(3-picolyl)aminocarbonyl) ethyl]benzamide (Yield: 76.3 %) as an opalescent solid.

[0155]

mp: 168-170 ℃

1H NMR(DMSO-d6) δppm: 2.47-2.53(2H, m), 2.93(2H, t, J=7.3 Hz), 4.27(2H, d, J=5.9 Hz), 4.90(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=6.6 Hz), 7.28-7.35(1H, m), 7.33(2H, d, J=8.1 Hz), 7.49(1H, dd, J=2.1, 5.9 Hz), 7.89(2H, d, J=8.1 Hz), 8.39-8.44(3H, m), 9.62(1H, br.s)

IR(KBr)cm-1: 3313, 1641, 1523, 1457, 1300, 748, 713

[0156]

Example 62

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl) methylaminocarbonyloxy]methylbenzamide (Table 1: Compound 85)

(62-1) To a solution of methyl 4-hydroxymethylbenzoate (1.99 g, 12.0

mmol) in THF (20 ml) were added 1.78 g of N,N'-carbonyldiimidazole (11.0 mmol) at room temperature, and the solution was stirred for an hour. To the solution were added 1.08 g of 3-picolylamine (10.0 mmol) at room temperature, and the mixture was stirred for 3.5 hours and left overnight. Water was added to the solution, and the mixture was extracted with ethyl acetate.

[0157]

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 2.76 g of N-(4-methoxycarbonyl) benzyloxycarbonyl-3-picolylamine (Yield: 91.9 %) as a white waxy solid.

1H NMR(CDCl3) δ ppm: 3.91(3H, s), 4.40(2H, d, J=5.9Hz), 5.18(2H, s), 5.5(1H, br.s), 7.24-7.28(1H, m), 7.40(2H, d, J=8.1 Hz), 7.65(1H, d, J=7.3 Hz), 8.02(2H, d, J=8.8 Hz), 8.50-8.53(2H, m)

[0158]

(62-2) To a suspension of 2.40 g of the compound from the process (62-1) (8.0 mmol) in methanol (10 ml) and water (20 ml) was added 0.42 g of lithium hydroxide monohydrate (10.0 mmol), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 10 % hydrochloric acid to acidified to pH 2 to 4, and the precipitated solid was collected by filtration and dried to give 1.83 g of N-(4-carboxy) benzyloxycarbonyl-3-picolylamine (79.9 %) as a white solid.

1H NMR(DMSO-d6) δ ppm: 4.24(2H, d, J=5.9 Hz), 5.13(2H, s), 7.33-7.38 (1H, m), 7.46(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 7.95-8.01(1H, m), 8.46(1H, d, J=5.1 Hz), 8.49(1H, d, J=1.5 Hz), 13.0(1H, br.s)

[0159]

(62-3) To a suspension of 1.26 g of the compound from the process (62-2) (4.4 mmol) in dichloromethane (20 ml) were slowly added 1.0 ml of oxalyl chloride (11.4 mmol) and then several drops of DMF. The reaction mixture was stirred at room temperature for 10 min. and at 40 ℃ for additional 30 min. After cooling, the mixture was evaporated and the excess oxalyl chloride was removed by evaporation with toluene. To the residue was added dichloromethane (10 ml). Under ice-cooling, to the mixture was then added dropwise a solution of 0.83 g of the compound from Example 1, the process (1-2) (4.0 mmol) in dichloromethane (8 ml) and pyridine (8 ml), and

the solution was warmed to room temperature with stirring for 7 hours and left overnight.

[0160]

To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. Toluene was added to the residue to azeotropically remove the excess pyridine. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 1.40 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methylaminocarbonyloxy]methylbenzamide (Yield: 73.4 %) as a light brown solid.

1H NMR (CDCl3) δ ppm: 1.51(9H, s), 4.40(2H, d, J=5.9 Hz), 5.19(2H, s), 5.56(1H, m), 7.07(1H, br.s), 7.14-7.31(4H, m), 7.43(2H, d, J=8.1 Hz), 7.65(1H, d, J=8.1 Hz), 7.76(1H, d, J=7.3 Hz), 7.95(2H, d, J=8.1 Hz), 8.52(2H, d, J=4.1 Hz), 9.32(1H,br.s)

[0161]

(62-4) To a solution of 1.00 g of the compound from the process (62-3) (2.10 mmol) in dioxane (10 ml) and methanol (2 ml) was added 4N hydrochloric acid-dioxane (9 ml) at room temperature, and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate aq. and the mixture was extracted with ethyl acetate-methyl ethyl ketone (1:1). The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.79 g of N-(2-aminophenyl)
-4-[(pyridin-3-yl)methylaminocarbonyloxy]methylbenzamide (Yield: quantitative) as a white solid.

mp: 139-141 ℃

1H NMR(DMSO-d6) δ pm: 4.25(2H, d, J=5.9 Hz), 4.90(2H, s), 5.13(2H, s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.47(2H, d, J=8.1 Hz), 7.67(1H, d, J=8.1 Hz), 7.97(2H, d, J=7.3 Hz), 7.9-8.0(1H, m), 8.46(1H, dd, J=1.5, 5.1 Hz), 8.49(1H, d, J=2.1 Hz), 9.65(1H, br.s)

IR(KBr)cm-1: 3326(br.), 1694, 1637, 1526, 1458, 1147, 750, 712

[0162]

Example 63

Preparation of N-(2-aminophenyl)-4-[3-(imidazol-1-yl) propylaminocarbonyloxy]methylbenzamide (Table 1: Compound 146)

The titled compound was prepared as described in Example 62.

mp: (amorphous)

1H NMR(270 MHz, DMSO-d6) δppm: 1.80-1.89(2H, m), 2.94-3.02(2H, m), 3.98(2H, t, J=7.3 Hz), 4.88(2H, s), 5.11(2H, s), 6.55-6.63(1H, m), 6.76-6.97(3H, m), 7.10-7.18(2H, m), 7.43-7.48(3H, m), 7.61(1H, s), 7.98(2H, d, J=8.1 Hz), 9.66(1H, s)

[0163]

Example 64

N-(2-aminophenyl)-4-(phenylacetylamino)benzamide

(Table 1: Compound 2)

(64-1) To a solution of the compound from Example 1, the process (1-2) (4.16 g, 20.0 mmol) in dichloromethane (30 ml) was added triethylamine (4.2 ml, 30.0 mmol) and then, was slowly added a solution of 4-nitrobenzoyl chloride (4.00 g, 21.6 mmol) in dichloromethane (10 ml), and the solution was stirred for 7 hours. To the solution was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

[0164]

The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate aq. and saturated brine; dried; and evaporated. The residue was washed with diisopropyl ether to give N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-nitrobenzamide (7.02 g, Yield: 98.3 %) as a light yellow solid.

1H NMR(270 MHz, CDCl3) δppm: 1.53(9H, s), 7.17-7.29(4H, m), 7.85(1H, br.d, J=7.3 Hz), 8.17(2H, d, J=8.8 Hz), 8.32(2H, d, J=8.8 Hz), 9.88(1H, br.s)

[0165]

(64-2) To a solution of the compound from the process (64-1) (6.00 g, 16.8 mmol) in THF (20 ml) and methanol (20 ml) was added 10 % Pd/C (wet, 0.6 g) in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. After cease of absorption of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated. To the residue were added diisopropyl ether and ethyl acetate, and the precipitated solid was

collected by filtration and dried to give N-[2-(N-tert-butoxycarbonylamino) phenyl]-4-aminobenzamide (4.74 g, Yield: 86.2 %) as a white solid.

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.46(9H, s), 5.84(2H, s), 6.61(2H, d, J=8.8 Hz), 7.10-7.18(2H, m), 7.46-7.55(2H, m), 7.68(2H, d, J=8.8 Hz), 8.67(1H, s), 9.49(1H, s)

[0166]

(64-3) To a solution of 1.6 g of the compound from the process (64-2) (4.88 mmol) in dichloromethane (15 ml) were added 0.8 ml of pyridine (9.9 mmol) and 0.96 ml of phenylacetyl chloride (7.26 mmol), and the solution was stirred for one day. After completion of the reaction, water was added and the precipitated crystals were collected by filtration to give 1.66 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-(phenylacetylamino)benzamide (Yield: 76 %).

[0167]

(64-4) To a solution of 1 g of the compound from the process (64-3) (2.24 mmol) in acetonitrile (25 ml) was added 0.88 ml of iodotrimethylsilane (6.18 mmol) at room temperature, and the solution was stirred for 3 hours. After completion of the reaction, the solution was concentrated. The residue was recrystallized from methanol to give 0.29 g of N-(2-aminophenyl)-4-(phenylacetylamino)benzamide (38 %) as white crystals.

[0168]

mp: 232-237 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.69(2H, s), 4.90(2H, s). 6.60(1H, t, J=7.35), 6.77(1H, d, J=7.35), 6.96(1H, t, J=7.35), 7.15(1H, d, J=7.35), 7.22-7.35(5H, m), 7.72(2H, d, J=8.80), 7.95(2H, d, J=8.80), 9.57(1H, s), 10.43(1H, s)

IR(KBr): 2937, 2764, 1660, 1598, 1506, 1459

[0169]

As described in Example 64, the compounds of Examples 65 to 76 were prepared, each of whose melting point (mp), 1H NMR data, IR data are shown below.

Example 65

N-(2-aminophenyl)-4-(4-phenylbutanoyl)aminomethylbenzamide

(Table 1: Compound 4)

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.91(2H, hep, J=7.3 Hz), 2.37(2H, t,

J=7.3 Hz), 2.64(2H, t, J=7.3 Hz), 5.0(2H, br.s), 6.61(1H, t, 7Hz), 6.79(1H, dd, J=1.5, 8.1Hz), 6.97(1H, t, J=7 Hz), 7.1-7.4(6H,m), 7.71(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.8 Hz), 9.57(1H, s), 10.15(1H, s)

IR(KBr)cm-1; 3344, 1687, 1603, 1542, 1460, 1315, 1033, 842, 737

[0170]

Example 66

N-(2-aminophenyl)-4-[(4-chlorophenylacetyl)amino]benzamide (Table 1: Compound 15)

mp:>250 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.72(2H, s), 7.29-7.43(8H, m), 7.77(2H, d, J=8.8), 8.00(2H, d, J=8.80), 10.29(1H, s), 10.52(1H, s)

IR(KBr)cm-1: 3300, 2868, 1664, 1638, 1520

[0171]

Example 67

N-(2-aminophenyl)-4-[(2-nitrophenylacetyl)amino]benzamide hydrochloride (Table 1: hydrochloride of Compound 19)

mp: >250℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.20(2H, s), 7.20-7.30(3H, m), 7.40-7.45(1H, m), 7.60(2H, d), 7.71-7.77(3H, m), 8.02-8.10(4H, m), 10.27(1H, br.s), 10.64(1H,br.s)

IR(KBr)cm-1: 3263, 1676, 1647, 1518, 1184, 759

[0172]

Example 68

N-(2-aminophenyl)-4-[(4-nitrophenylacetyl)amino]benzamide (Table 1: Compound 21)

mp: 222-226 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.90(2H, s), 4.96(2H, br.s), 6.60(1H, dt, J=1.47, 6.61), 6.78(1H, dd, J=1.47, 6.61), 6.97(1H, dt, J=1.47, 6.61), 7.15(1H, dd, J=1.47, 6.61), 7.63(2H, d, J=8.80), 7.71(2H, d, J=8.80), 7.95(2H, d, J=8.80), 8.22(2H, d, J=8.80), 9.59(1H, s), 10.54(1H, s).

IR(KBr)cm-1: 3395, 3334, 1671, 1630, 1519, 1346

[0173]

Example 69

N-(2-aminophenyl)-4-[(2-aminophenylacetyl)amino]benzamide (Table

1: Compound 22)

mp: 177-182 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 3.54(2H, s), 4.88(2H, br.s), 5.09(2H, br.s), 6.55(1H, dd, 6.6, 7.3), 6.59(1H, dd, 7.3, 7.3), 6.68(1H, d, 7.3), 6.78(1H, d, 7.3), 6.96(2H, dd, 7.3, 7.3), 7.06(1H, d, 6.6), 7.15(1H, d, 7.3), 7.71(2H, d, 8.8), 7.95(2H, d, 8.8), 9.57(1H, br.s), 10.39(1H, br.s)

IR(KBr)cm-1: 3374, 3256(br.), 1683, 1597, 1503, 1317, 1262, 1180, 1153, 747

[0174]

Example 70

N-(2-aminophenyl)-4-[(4-aminophenylacetyl)amino]benzamide (Table 1: Compound 26)

mp: 219-226 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 3.46(2H, s), 4.93(4H, br.s), 6.52(2H,d, J=8.07), 6.59(1H, dt, J=1.47, 7.34), 6.77(1H, dd, J=1.47, 7.35), 6.97(1H, dt, J=1.47, 7.35), 6.99(2H, d, J=8.07), 7.15(1H, dd, J=1.47, 7.35), 7.70(2H, d, J=8.80), 7.93(2H, d, J=8.80)

IR(KBr)cm-1: 3278, 3032, 1675, 1628, 1516

[0175]

Example 71

N-(2-aminophenyl)-4-[(4-methoxyphenylacetyl)amino]benzamide (Table 1: Compound 32)

mp: >250℃

1H NMR(270 MHz, DMSO-d6) δppm: 3.62(2H, s), 3.74(3H, s), 6.90(2H, d, J=8.80), 7.26(2H, d, J=8.80), 7.30(3H, m), 7.39(1H, m), 7.77(2H, d, J=8.80), 7.99(2H, d, J=8.80), 10.26(1H, s), 10.44(1H, s)

IR(KBr)cm-1: 3300, 2759, 1670, 1638, 1514, 1250

[0176]

Example 72

N-(2-aminophenyl)-4-[(4-(N,N-dimethylamino)phenylacetyl)amino]benzamide (Table 1: Compound 157)

mp: 140 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 3.04(6H, s), 3.67(2H, s), 7.16(2H, d, J=8.08), 7.29-7.40(6H, m), 7.76(2H, d, J=8.80), 7.99(2H, d, J=8.80), 10.29(1H, s), 10.47(1H, s)

IR(KBr)cm-1: 3244, 2951, 2639, 1647, 1599, 1507

[0177]

Example 73

N-(2-aminophenyl)-4-[(4-trifluoromethylphenylacetyl)amino]benzamide (Table 1: Compound 43)

mp: >250℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(2H, s), 6.89(1H, t, J=7.35), 7.00(1H, d, J=7.35 Hz), 7.11(1H, t, J=7.35), 7.25(1H, d, J=7.35), 7.57(2H, d, J=8.80), 7.71(2H, d, J=8.80), 7.73(2H, d, J=8.80), 7.97(2H, d, J=8.80), 9.87(1H, s), 10.54(1H, s)

IR(KBr)cm-1: 3260, 1664, 1605, 1521, 1327, 1119

[0178]

Example 74

N-(2-aminophenyl)-4-[(pyridin-2-yl)acetoamino]benzamide dihydrochloride(Table 1: hydrochloride of Compound 54)

mp: 154-175℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.60(2H, s), 7.30-7.46(3H, m), 7.56(1H, d, J=7.35), 7.79(2H, d, J=8.80), 7.95(1H, t, J=6.61), 8.01(1H, d, J=7.35), 8.11(2H, d, J=8.80), 8.49(1H, t, J=7.35), 8.87(1H, d, J=5.14), 10.46(1H, s)

[0179]

Example 75

N-(2-aminophenyl)-4-[(pyridin-3-yl)acetoamino]benzamide dihydrochloride(Table 1: hydrochloride of Compound 68)

mp: 182-189 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.12(2H, s), 7.29-7.59(4H, m), 7.80(2H, d, J=8.80), 8.05(1H, m), 8.11(2H, d, J=8.80), 8.57(1H, d, J=8.08), 8.85(1H, d, J=5.15), 8.95(1H, s), 10.25(1H, s), 10.48(1H, s)

[0180]

Example 76

N-(2-aminophenyl)-4-[(3-(pyridin-3-yl)propanoyl)amino]benzamide (Table 1: Compound 69)

mp: 184-186 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.80(2H, t, J=7.34), 3.08(2H, t, J=7.34), 6.87(1H, t, J=8.07), 6.99(1H, dd, J=1.47, 8.07), 7.11(1H, dt, J=1.47, 8.07),

7.25(1H, d, J=8.07), 7.70(2H, d, J=8.80), 7.77(1H, dd, J=5.87, 8.07), 7.96(2H, d, J=8.80), 8.22(1H, d, J=8.07), 8.75(1H, d, J=1.47), 9.83(1H, s), 10.25(1H, s)

[0181]

Example 77

Preparation of N-(2-aminophenyl)-4-(N-benzylamino) carbonylbenzamide (Table 1: Compound 8)

(77-1) To a suspension of monomethyl terephthalate (13.0 g, 72.2 mmol) in toluene (100 ml) was added dropwise thionyl chloride (10 ml) at room temperature. After stirring at 80 ℃ for 3 hours, the solvent and an excess amount of thionyl chloride were removed by evaporation. The residue was suspended in dioxane (100 ml), and 2-nitroaniline (9.98 g, 72.2 mmol) were added to the suspension, followed by refluxing with heating for 4 hours.

[0182]

After cooling and evaporation, the residue was washed with methanol to give N-(2-nitrophenyl)-4-methoxycarbonylbenzamide (20.3 g, Yield: 93.7 %) as a yellow solid.

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.91(3H, s), 7.43-7.49(1H, m), 7.76-7.78(2H, m), 8.03(1H, d, J=8.1), 8.08(2H, d, J=8.8 Hz), 8.14(2H, d, J=8.8 Hz), 10.94(1H, s)

[0183]

(77-2) To a solution of the compound (4.24 g, 14.12 mmol) from the process (77-1) in THF (50 ml) and methanol (50 ml) was added 10 % Pd/C (0.4 g) in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with methanol to give N-(2-aminophenyl)-4-methoxycarbonylbenzamide (3.4 g, Yield: 87.5 %) as a light yellow solid.

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.90(3H, s), 4.95(2H, s), 6.60(1H, dd, J=7.3, 8.1), 6.78(1H, d, J=7.3), 6.99(1H, dd, J=7.3, 7.3), 7.17(1H, d, J=7.3), 8.08(2H, d, J=8.1), 8.11(2H, d, J=8.1), 9.85(1H, s)

[0184]

(77-3) To a solution of the compound from the process (77-2) (2.71 g, 10.0 mmol) in dioxane (100 ml) and water (50 ml) was added 5 % sodium hydroxide aq. under ice-cooling, and then were added dropwise di-tert-butyl

dicarbonate (2.62 g, 12.0 mmol) in dioxane (40 ml). The mixture was stirred at room temperature for 4 hours and left overnight. To the mixture were added saturated brine and ethyl acetate, and the two layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with methanol to give N-[2-(N-tert-butoxycarbonyl)amino]phenyl -4-methoxycarbonylbenzamide (3.54 g, Yield: 95.7 %) as a light brown solid.
1H NMR(270 MHz, DMSO-d6) δppm: 1.44(9H, s), 3.90(3H, s), 7.12-7.24(2H, m), 7.55-7.58(2H, m), 8.09(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.72(1H, s), 10.00(1H, s)

[0185]

(77-4) A suspension of the compound from the process (77-3) (3.00 g, 8.10 mmol) in methanol (50 ml) and 0.5N lithium hydroxide aq. (25 ml) was heated with stirring at 40 ℃ for 5 hours. After removing methanol by evaporation, to the residue was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with a small amount of water and saturated brine, dried and evaporated. The residue was washed with methanol to give terephthalic mono-2-(N-tert-butoxycarbonyl) aminoanilide (2.24 g, Yield: 77.6 %) as a light brown solid.
1H NMR(270 MHz, DMSO-d6) δ ppm: 1.45(9H, s), 7.12-7.21(2H, m), 7.53-7.58(2H, m), 8.06(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.71(1H, s), 9.97(1H, s)

[0186]

(77-5) To a suspension of the compound from the process (77-4) (0.20 g, 0.56 mmol) in dichloromethane (4 ml) were added benzylamine (0.14 g, 1.3 mmol) and then triethylamine (0.21 ml, 1.5 mmol). To the solution was added 0.25 g of 2-chloro-1,3-dimethylimidazolium chloride (1.48 mmol) under ice-cooling, and then the mixture was stirred under ice-cooling for an hour and at room temperature for an hour. After diluting with chloroform and adding water, the aqueous layer was extracted with chloroform.

[0187]

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:methanol = 10:1). The solid obtained was washed with

diethyl ether to give N-(2-tert-butoxycarbonylaminophenyl)
-4-(N-benzylamino)carbonylbenzamide (279 mg, Yield: 62.6 %) as a white solid.
1H NMR(270 MHz, DMSO-d6) δ ppm: 1.45(9H, s), 4.52(2H, d, J=5.8 Hz), 7.13-7.28 (4H, m), 7.34-7.35(3H, m), 7.56(2H, d, J=8.1 Hz), 8.05(4H, s), 8.71(1H, br.s), 9.23(1H, t), 9.94(1H, s)

[0188]

(77-6) To the compound from the process (77-5) (151 mg, 0.339 mmol) was added 4N hydrochloric acid-dioxane (5 ml) at room temperature, and the mixture was stirred for 4 hours. After evaporation, the mixture was partitioned between ethyl acetate and saturated sodium bicarbonate aq. After removing the precipitate, the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diethyl ether, and the precipitate was collected by filtration and dried to give N-(2-aminophenyl)-4-(N-benzylamino) carbonylbenzamide (78 mg, 67 %) as a white solid.

mp: 239-241 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.51(2H, s), 4.93(2H, br.d), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.95(1H, dd, J=7.3, 8.3 Hz), 7.18(1H, d), 7.23-7.35(5H, m), 8.01, 8.07 (4H, d, J=8.8 Hz), 9.22(1H, br.t), 9.81(1H, br.s)

[0189]

As described in Example 77, the compound of Example 78 was prepared, whose melting point (mp), 1H NMR data, IR data are shown below.

[0190]

Example 78

N-(2-aminophenyl)-4-[N-(2-phenylethyl)amino]carbonylbenzamide (Table 1: Compound 9)

mp: 237-240 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.87(2H, t, 7.3), 3.51(2H, dt, 5.9, 7.3), 4.94(2H,br.s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 7.3), 6.98(1H, dd, 7.3, 7.3), 7.15-7.34(6H, m), 7.93(2H, d, 8.1), 8.04(2H, d, 8.1), 8.73(1H, t, 5.1), 9.76(1H, br.s)

IR(KBr)cm-1: 3396, 3320, 1625, 1602, 1539, 1458, 1313, 699

[0191]

Example 79

Preparation of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)amino] benzamide (Table 1: Compound 158)

(79-1) To a solution of 3 g of the compound from Example 64, the process (64-2) (9.2 mmol) and 2.16 g of 4-nitrophenoxyacetic acid (11.0 mmol) in DMF (7 ml) were added 2.82 g of dicyclohexylcarbodiimide (13.8 mmol) in DMF (5 ml) and a catalytic amount of N,N-dimethylaminopyridine, and the mixture was stirred for one day. After completion of the reaction, ethyl acetate was added to the mixture, insolubles were filtered out through celite, and the solvent was removed by evaporation.

[0192]

The residue was recrystallized from chloroform to give 2.34 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-nitrophenoxyacetyl)amino]benz amide (Yield: 50 %).

1H NMR(270 MHz, DMSO-d6) δppm: 1.45(9H, s), 4.97(2H, s), 7.12-7.26(3H, m), 7.23(2H, d, J=8.80), 7.53(1H, dt, J=2.20, 7.35), 7.79(2H, d, J=8.80), 7.95(2H, d, J=8.80), 8.25(2H, d, J=8.80), 8.71(1H, s), 9.79(1H, s), 10.52(1H, s)

[0193]

(79-2) To a solution of 0.7 g of the compound from the process (79-1) (1.38 mmol) in acetonitrile (10 ml) was added 1.26 ml of iodotrimethylsilane (8.85 mmol) at room temperature, and the solution was stirred for 2 hours. After completion of the reaction, the solution was concentrated and ethyl acetate was added. The solution was stirred for 20 min, and the precipitated crystals were collected by filtration. The crystals were dissolved in methyl ethyl ketone. The solution was washed with saturated sodium thiosulfate aq. and saturated brine in sequence, dried out with anhydrous magnesium sulfate, and evaporated. The residue was washed with ethyl acetate to give 0.22 g of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)
amino]benzamide (Yield: 39 %) as white crystals.

mp: 212-215 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.97(2H, s), 6.88(1H, t, J=7.35), 6.99(1H, d, J=7.35), 7.11(1H, t, J=7.35), 7.23(2H,d, J=8.80), 7.24(1H, 1H, m), 7.77(2H, d, J=8.80), 8.00(2H, d, J=8.80), 8.25(2H, d, J=8.80), 9.89(1H, s), 10.52(1H, s)

IR(KBr)cm-1: 3382, 3109, 1650, 1591, 1508, 1341

[0194]

Example 80

Preparation of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl) amino]benzamide (Table 1: Compound 159)

To a solution of 1.41 g of the compound from Example 79, the process (79-1) (2.78 mmol) in methanol (15 ml) and THF (25 ml) was added 10 % Pd-C, and the mixture was stirred in an atmosphere of hydrogen, at room temperature for an hour. After completion of the reaction, the catalyst was filtered out and the filtrate was concentrated. The residue was triturated with diisopropyl ether to give 1.1 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-aminophenoxyacetyl)amino]benzamide.

[0195]

The product was dissolved in 15 ml of acetonitrile. To the solution was added 0.74 ml of iodotrimethylsilane (5.20 mmol), and the mixture was stirred at room temperature for 3 hours. After completion of the reaction, the mixture was evaporated. The residue was washed with methyl ethyl ketone to give 0.86 g of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl)amino]benzamide (Yield: 83 %).

mp: (amorphous)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.82(2H, s), 7.13(2H, d, J=8.80), 7.30-7.48 (6H, m), 7.82(2H, d, J=8.80), 8.03(2H, d, J=8.80), 10.34(1H, s), 10.46(1H, s)

IR(KBr)cm-1: 2873, 2590, 1680, 1602, 1505, 1243

[0196]

Pharmacological test example 1

Test for induction of differentiation in A2780 cells

Increase of alkaline phosphatase (ALP) activity is known as an indicator for differentiation of human colon cancer cells. For example, it is known that sodium butylate may increase ALP activity (Young et al., Cancer Res., 45, 2976(1985); Morita et al., Cancer Res., 42, 4540(1982)). Thus, differentiation inducing action was evaluated using ALP activity as an indicator.

[0197]

(Experimental procedure)

To each well of a 96-well plate was inoculated 0.1 ml of A2780 cells (15,000 cells/well) and on the next day was added 0.1 ml of a stepwise diluted test compound solution with the medium. After incubation for 3 days, the cells on the plate were washed twice with a TBS buffer (20 mM Tris, 137 mM NaCl, pH 7.6). Then, to each well was added 0.05 ml of 0.6 mg/ml p-nitrophenylphosphate (9.6 % diethanolamine, 0.5 mM $MgCl_2$ (pH 9.6)) solution, and the plate was incubated at room temperature for 30 min. The reaction was quenched with 0.05 ml/well of 3N sodium hydroxide aq. For each well, an absorbance at 405 nm was measured to determine the minimum concentration of the drug inducing elevation of ALP activity (ALPmin).

(Experimental Results)

The results are shown in Table 2.

[0198]

Table 2: Effect for induction of differentiation in A2780 cells

Test Compound	ALPmin(μM)
Compound in Example 4	1
Compound in Example 5	1
Compound in Example 8	1
Compound in Example 9	1
Compound in Example 10	3
Compound in Example 11	1
Compound in Example 13	1
Compound in Example 15	3
Compound in Example 16	3
Compound in Example 18	3
Compound in Example 23	1
Compound in Example 24	1
Compound in Example 25	3
Compound in Example 26	1
Compound in Example 27	10
Compound in Example 28	10
Compound in Example 29	10
Compound in Example 30	0.1
Compound in Example 31	0.1
Compound in Example 32	0.1
Compound in Example 33	1
Compound in Example 34	1
Compound in Example 35	1
Compound in Example 36	3
Compound in Example 37	3
Compound in Example 38	1
Compound in Example 39	1
Compound in Example 40	3
Compound in Example 41	3
Compound in Example 42	3
Compound in Example 43	3

Compound in Example 44	3
Compound in Example 47	3
Compound in Example 48	3
Compound in Example 49	3
Compound in Example 50	3
Compound in Example 51	3
Compound in Example 52	3
Compound in Example 53	30
Compound in Example 54	0.1
Compound in Example 55	0.3
Compound in Example 56	3
Compound in Example 57	0.1
Compound in Example 58	3
Compound in Example 59	3
Compound in Example 60	10
Compound in Example 61	0.1
Compound in Example 62	0.1
Compound in Example 63	3
Compound in Example 64	1
Compound in Example 66	3
Compound in Example 68	1
Compound in Example 70	1
Compound in Example 71	1
Compound in Example 72	3
Compound in Example 73	1
Compound in Example 74	3
Compound in Example 75	3
Compound in Example 76	0.1

[0199]

Pharmacological test example 2

Antitumor action test

(Experimental procedure)

To a nude mouse was inoculated tumor cells subcutaneously subcultured in a nude mouse (HT-29, KB-3-1). When the volume became about

20 to 100 mm^3 and take was confirmed, administration of a drug was initiated. This day was Day 1, and subsequently the drug was orally administered in Day 1 to 5, in Day 8 to 12, Day 15 to 19 and in Day 22 to 26.

The volume of the tumor was determined from the following equation:

(Volume of a tumor) = 1/2 x (major axis) x (minor axis)^2

(Experimental Results)

The results for the compound of Example 32 (dose: 66 μ mol/kg) against HT-29 are shown in Figure 1.

[0201]

The results for the compound of Example 32 (dose: 66 μ mol/kg) against KB-3-1 are shown in Figure 2.

[Effects of the Invention]

The novel benzamide edrivative of the present invention has differenciation-inducing effect and is useful for medical and pharmaceutical products. In particular, it has high effect as an anticancer drug, is effective against hematologic malignancy and solid tumors.

[Brief Description of the Drawings]

[Fig.1]

It shows a change of the volume of the tumor when the compound of Example 32 was administered against the tumor cell HT-29.

[Fing.2]

It shows a change of the volume of the tumor when the compound of Example 32 was administered against the tumor cell KB-3-1.